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TITLE: Development of a lifespan-based novel composite person-reported outcome measure using data from the CINRG Duchenne natural history study

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14. ABSTRACT Development of novel technologies and therapeutic agents to treat Duchenne muscular dystrophy (DMD) have increased interest by regulatory bodies such as the Food and Drug Administration in the development of "clinically-meaningful" study endpoints for clinical trials. There is a need for the development of person-reported outcome (PRO) instruments that target a broad range of developmental and functional ability while effectively evaluating treatment effects in clinical trials. Our proposed project will use quality of life questionnaire data from the first 4-7 years of ongoing Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study. Using that data, we will identify questions that show differences between people with different levels of abilities (such as those who can walk or just raise a hand to the mouth), or that show changes over one year that might be seen by researchers during drug clinical trials. Those questions will then be combined and built into a computerized adaptive testing (CAT) system that will produce short, individualized surveys for clinical practice and clinical trial use that are tailored to a patients' level of functional ability.					
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1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

Background: Development of novel technologies and therapeutic agents to treat Duchenne muscular dystrophy (DMD) have increased interest by regulatory bodies such as the Food and Drug Administration in the development of “clinically-meaningful” study endpoints for clinical trials. There is a need for the development of person-reported outcome (PRO) instruments that target a broad range of developmental and functional ability while effectively evaluating treatment effects in clinical trials.

Objective: Our proposed project will use quality of life questionnaire data from the first 4-7 years of ongoing Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study. Using that data, we will identify questions that show differences between people with different levels of abilities (such as those who can walk or just raise a hand to the mouth), or that show changes over one year that might be seen by researchers during drug clinical trials. Those questions will then be combined and built into a computerized adaptive testing (CAT) system that will produce short, individualized surveys for clinical practice and clinical trial use that are tailored to a patients’ level of functional ability.

Applicability: Well-designed CAT-PRO questionnaires can be used in both clinical trials and day-to-day clinical practice. For clinical trials, they provide researchers with the ability to put all patients, regardless of their functional abilities, together on the same scale. That means that one tool can be used to evaluate quality of life across many types of studies and many groups of patients, but that the results can still be compared. Those results can then also be compared to other clinical trial measures such as strength tests, timed function tests, or pulmonary function tests to help teach researchers and regulatory authorities about how “in clinic” tests commonly used in clinical trials relate to a persons’ quality of life, and whether those tests are “clinically meaningful”. In day-to-day clinical practice, it means that doctors can have a single tool that can give feedback on a patient’s quality of life, even as their levels of ability change over time. Within 3 years, this project will be able to produce such a useful tool because much of the data has already been collected from the CINRG study and because the rest of the data will be from the large group of over 3000 volunteers who are already part of the Parent Project Muscular Dystrophy DuchenneConnect Registry.

Impact and Contributions: Data from the CINRG DMD natural history study cohort and the DuchenneConnect Registry will provide the basis for development of a “clinical trial-ready” novel CAT-based PRO measure that has been constructed against a background of comprehensive clinical assessments of strength and function across the DMD lifespan. This PRO measure will be rapidly usable as a sensitive measure for use in the growing field of DMD clinical trials, and will help to demonstrate “clinically meaningful” results to regulatory agencies in charge of new drug approval.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

Duchenne muscular dystrophy
Person-reported outcomes
Health-related quality of life
Functional health assessment
UC Davis / CINRG Duchenne Natural History Study

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Background: Development of novel technologies and therapeutic agents to treat Duchenne muscular dystrophy (DMD) have increased interest by regulatory bodies in the development of “clinically-meaningful” study endpoints for clinical trials. There is a need for the development of person-reported outcome (PRO) instruments that target a broad range of developmental and functional ability while retaining enough resolution to effectively evaluate treatment effects.

Objective: Our proposed project will use historical data and RASCH analysis techniques to identify a hierarchical PRO “item bank” of questions that can be applied across the DMD lifespan. In addition, we will create a computerized adaptive testing (CAT) format to simplify administration in clinical trials. We will identify changes in person reported QoL using the new composite tool that occur when “milestone” functions, such as standing from the floor, climbing stairs, rising from a chair, walking independently, raising arms overhead, raising a hand to the mouth, and cough independently are lost.

Specific Aims:

Aim 1 (66% complete): In the *first year* of the project, we will use RASCH analysis techniques to analyze PRO measure item responses to develop a novel DMD-specific composite PRO measure that measure multiple domains and spans the entire spectrum of DMD severity and progression.

Aim 1.1 (Complete): Using all available PRO data, we will evaluate item responses across domains to develop domain-specific item banks for a composite PRO measure.

Aim 1.2 (Complete): We will identify ranges of function where overlapping PRO items or gaps in item content exist against a backdrop of the entire range of meaningful functional abilities demonstrated by the DMD population across all age groups.

Aim 1.3 (In progress): We will conduct focus group discussions to identify relevant items for inclusion in a composite PRO measure, and to develop new items where suitable ones do not exist.

Aim 2: In the *second year* of the project, we will administer the resulting item banks of the new composite PRO measure to the 420 surviving CINRG Duchenne natural history study participants, as well as to participants in the Parent Project Muscular Dystrophy DuchenneConnect registry. Using the resulting short-term longitudinal pilot data from both cohorts, we will:

Aim 2.1: Test the newly derived item banks to validate the hierarchy established by the year-1 Rasch analysis.

Aim 2.2: Confirm responsiveness of the composite PRO to changes in self-reported functional milestone abilities.

Aim 3: In the *third year* of the project, we will use Year 2 pilot data to develop a brief computerized adaptive testing (CAT) version of the new composite PRO instrument, and we will make it available to the clinical research community for inclusion in natural history studies and clinical trials for persons with DMD.

Study Design: We will conduct a retrospective analysis of 4-7 years of longitudinal multicenter PRO data from 420 patients/families enrolled in the CINRG Duchenne natural history study representing 1600+ person-years of follow up. Banks of question items responsive to differences in functional ability or disease progression over 1 year will be evaluated prospectively in partnership with the DuchenneConnect patient registry. Resulting data will be used to construct a responsive CAT-based PRO measure for use across multiple ages/stages of disease.

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Following a significant initial delay in receipt of the PRO dataset from the CINRG group, we received the data and completed Aims 1-1.2 of our project. Output of these activities included:

- human subject review with a resulting exemption for use of de-identified retrospective data;
- review of PRO item responsiveness characteristics;
- development of responsive item sets within the mobility domain defined by the World Health Organization ICF framework;
- factor analysis of responsive item sets;
- initial Rasch analysis of mobility-associated item sets;
- identification of floor and ceiling effects for resulting item sets;
- cross-linking of item sets with items from commonly employed clinically-reported outcome measures (ClinROs);
- refinement of item syntax and presentation based on item response characteristics;
- development of pilot item sets for evaluation by expert and patient focus groups, including possible items to include to address floor and ceiling effects; and
- initial recommendations for composite scale scoring methods

An excerpt from the detailed study report is provided below. Now that content to be presented has been defined, we are developing human subject protocols for focus group discussions, for review by the UC Davis and DoD human subject review committees.

1.1 Results

Study Population: Four hundred and ten patient-parent/guardian pairs completed survey instruments and clinical evaluation testing. Full details on the content and timing of visits and the overall subject population have been previously published (Henricson, Abresch et al. 2013, McDonald, Henricson et al. 2013). Participants represented a wide range of ages representative of the disease (age at initial visit 11.3[5.7] years, range 4 – 28 years). The number of completed visits per participant ranged from 1 to 13 (mean 5[3]) with follow-up in some participants to month 96, for a total of 3066 completed visits. At baseline 125 (30%) of participants were glucocorticoid steroid-naïve, 49 (12%) were previous steroid users, and 236 (58%) were steroid users. At baseline 253 (62%) were ambulatory, and 47 (11%) had a forced vital capacity <30% of predicted for age.

Grouping Question Items by WHO-ICF Domains: We classified 367 question items according to the WHO-ICF domains for Function (Part B), Activities and Participation (Part D) and Environmental Factors (Part E), with each question being considered for inclusion under each construct. A summary of the number of items included in each construct and subdomain, by original instrument is included as Table V.2. When classified under the Function construct, 142 items were assigned to the Mental Function subdomain, 10 to the Sensory Functions and Pain subdomain, 8 to the

Functions of the Hematological, Immunological and Respiratory Systems subdomain, 148 to Neuromusculoskeletal and Movement-Related Functions subdomain, and one to the Functions of the Skin and Related Structures subdomain. Items were further subclassified under each subdomain as noted in Table V.2. When classified under the Activities and Participation construct, 12 items were assigned to the Learning and Applying Knowledge subdomain, 20 to General Tasks and Demands, 12 to Communications, 110 to Mobility, 60 to Self-Care, two to domestic life, 28 to Interpersonal Interactions and Relationships, 10 to Major Life Areas, and 26 to Community, Social and Civic Life. Under the Neuromusculoskeletal and Movement-Related Functions subdomain, we created further sub-classifications that represent domains from the Performance of the Upper Limb (PUL) (Mayhew, Mazzone et al. 2013) and North Star Ambulatory Assessment (NSAA) (Mayhew, Cano et al. 2011) clinical evaluations with the goal of subdividing self-report tasks according to existing models of upper limb function and ambulatory mobility. When classified under the Environmental Factors construct, 30 items were assigned to the Products and Technology subdomain, 10 to Natural Environment and Human-Made Changes to the Environment, 14 to Support and Relationships, two to attitudes, and 27 to Services, Systems and Policies.

Item Sensitivity to One-Year Change and Disease Progression: We evaluated each question item to evaluate whether it was able to detect differences between individuals of different functional milestone groups, and its ability to demonstrate significant change in a one-year period of time consistent with the duration of most contemporary clinical trials. Taken together, item responsiveness screening yielded a list of 138 of the original 367 question items (37.6%). A summary of the numbers and percent of sensitive question items by WHO-ICF domain/subdomain and instrument is presented in Table V.2. In the Function construct, only a very small number of questions in the Mental Functions subdomain (0.4%) and none of the items in the Functions of the Skin and Related Structures subdomain met criteria for being responsive. Approximately half of the items in the Sensory Functions and Pain (40%) and Functions of the Cardiovascular, Hematological, Immunological and Respiratory Systems subdomains (50%) demonstrated responsiveness. Three quarters (75%) of items assigned to the Neuromuscular and Movement-Related Functions subdomain demonstrated responsiveness. In the Activities and Participation construct, relatively small percentages of items demonstrated responsiveness in the Learning and Applying Knowledge subdomain (25%), General Tasks and Demands (5%), Interpersonal Interactions and Relationships (11%), Major Life Areas (0%), and Community, Social and Civic Life (27%). Approximately half of items in the Communication subdomain (50%), Self Care (53%) and Domestic Life (50%) demonstrated responsiveness, although the latter was comprised of a single item. Of 110 items initially assigned to the Mobility subdomain, 74 (67%) demonstrated responsiveness to disease stage and progression over time. The percentage of responsive items in the Environmental Factors construct subdomains varied, representing none (0%) in Attitudes, 11% in Services, Systems and Policies, 21% in Support and Relationships, 30% in Natural Environment and Human-Made Changes to the Environment, and 50% in Products and Technology.

Table V.2

Responsive Items / All Items by WHO-ICF Domain and Instrument (#/%)									
Domain/Subdomain	LSI-A	NeuroQoL	PedsQL	PedsQL NMM	POSNA PODCI	PSQI	SF-36	WHO-QoL	All Instruments
ICF Part B: Function									
Subdomain: Mental Function									6/142 (0.4%)
Intellectual Function	0/3 (0%)		0/1 (0%)						0/4 (0%)
Temperament and Personality Functions	0/9 (0%)		0/1 (0%)		0/1 (0%)				0/11 (0%)
Energy and Drive Functions	0/4 (0%)	0/17 (0%)	1/1 (100%)	0/2 (0%)	0/2 (0%)	0/1 (0%)	0/4 (0%)	0/1 (0%)	1/32 (3%)
Sleep Functions		0/1 (0%)	0/1 (0%)	1/1 (100%)		3/10 (30%)			4/13 (31%)
Attention Functions			0/1 (0%)					0/1 (0%)	0/2 (0%)
Memory Functions			0/1 (0%)						0/1 (0%)
Emotional Functions: Anxiety		0/13 (0%)	0/1 (0%)				0/2 (0%)		0/16 (0%)
Emotional Functions: Depression	0/2 (0%)	0/13 (0%)	0/1 (0%)				0/3 (0%)	0/2 (0%)	0/21 (0%)
Emotional Functions: Fear	0/1 (0%)	0/3 (0%)	0/1 (0%)						0/5 (0%)
Emotional Functions: Frustration	0/2 (0%)		0/1 (0%)						0 (0%)
Emotional Functions: Satisfaction	0/14 (0%)	0/1 (0%)			1/5 (20%)			0/14 (0%)	1/34 (3%)
Subdomain: Sensory Functions and Pain									4/10 (40%)
Sensory Functions and Pain			1/1 (100%)	1/2 (50%)	0/3 (0%)	2/3 (66%)		0/1 (0%)	4/10 (40%)
Subdomain: Functions of the Cardiovascular, Hematological, Immunological and Respiratory Systems									4/8 (50%)
Functions of the Hematological and Immunological Systems				1/2 (50%)		0/2 (0%)			1/8 (25%)
Functions of the Respiratory System				1/2 (50%)					1/2 (50%)
Functions Related to the Digestive System				1/1 (100%)					1/1 (100%)
Functions Related to Metabolism and the Endocrine System				1/1 (100%)					1/1 (100%)
Subdomain: Neuromusculoskeletal and Movement-Related Functions									112/148 (75%)
PUL High Level: Shoulder Dimension		7/11 (64%)	1/1 (100%)		6/8 (75%)				14/20 (70%)
PUL Mid-Level: Elbow Dimension		14/18 (77%)		0/1 (0%)	3/3 (100%)				17/22 (22%)
PUL Distal-Level: Wrist and Finger Dimension		8/11 (73%)		2/2 (100%)	1/1 (100%)				11/14 (79%)
Complex: Standing from Supine		2/3 (66%)							2/3 (67%)
Complex: Standing from Seated		6/7 (86%)			1/1 (100%)				7/8 (88%)
Complex: Transfers		7/10 (70%)		1/1 (100%)	1/1 (100%)				9/12 (75%)
Head/Neck		1/1 (100%)							1/1 (100%)
Trunk: Standing		6/7 (86%)	1/1 (100%)	1/1 (100%)	1/1 (100%)				9/10 (90%)
Trunk: Sitting		6/8 (75%)			4/4 (100%)				12/12 (100%)
LL: Running		0/6 (0%)	2/2 (100%)		4/5 (80%)				6/13 (46%)
LL: Climbing		2/7 (29%)			3/3 (100%)				5/10 (50%)
LL: Walking		12/15 (80%)	2/3 (66%)		5/5 (100%)				19/23 (83%)
Subdomain: Functions of the Skin and Related Structures									0/1 (0%)
Functions of the Skin and Related Structures				0/1 (0%)					0/1 (0%)
ICF Part D: Activities and Participation									
Subdomain: Learning and Applying Knowledge									3/12 (25%)
Learning and Applying Knowledge	0/3 (0%)	0/2 (0%)	2/5 (40%)		1/1 (100%)			0/1 (0%)	3/12 (25%)
Subdomain: General Tasks and Demands									1/20 (5%)
Undertaking Multiple Tasks	0/1 (0%)	0/3 (0%)							0/4 (0%)
Carrying Out a Daily Routine	0/3 (0%)	0/1 (0%)		1/1 (100%)	0/2 (0%)	0/2 (0%)		0/6 (0%)	1/15 (7%)
Handling Stress and Other Psychological Demands		0/1 (0%)							0/1 (0%)
Subdomain: Communication									6/12 (50%)
Communication	0/1 (0%)	5/7 (72%)		0/3 (0%)	1/1 (100%)				6/12 (50%)
Subdomain: Mobility									74/110 (67%)
Changing and Maintaining Body Position		19/21 (90%)		1/1 (100%)	8/8 (100%)				28/30 (93%)
Carrying, Moving and Handling Objects		13/24 (54%)	1/1 (100%)	2/2 (100%)	4/4 (100%)				20/31 (65%)
Walking and Moving		13/29 (45%)	2/2 (100%)		10/12 (83%)		0/1 (0%)		25/44 (57%)
Moving Around Using Transportation		0/3 (0%)			1/1 (100%)		0/1 (0%)		1/5 (20%)
Subdomain: Self-Care									32/60 (53%)
Washing Oneself		6/8 (75%)	1/1 (100%)	1/1 (100%)					8/10 (80%)
Caring for Body Parts	0/1 (0%)	3/4 (75%)			1/1 (100%)			0/1 (0%)	4/7 (57%)
Toileting		4/5 (80%)		1/1 (100%)					5/6 (83%)
Dressing		7/8 (88%)			2/2 (100%)				9/10 (90%)
Eating		1/2 (50%)		0/1 (0%)	1/1 (100%)				2/4 (50%)
Drinking		1/1 (100%)							1/1 (100%)
Looking After One's Health	0/1 (0%)			0/1 (0%)	0/6 (0%)	3/9 (33%)		0/5 (0%)	3/22 (14%)
Subdomain: Domestic Life									1/2 (50%)
Domestic Life		0/1 (0%)	1/1 (100%)						1/2 (50%)
Subdomain: Interpersonal Interactions and Relationships									3/28 (11%)
Informal Social Relationships	0/3 (0%)	1/6 (17%)	0/5 (0%)		0/3 (0%)			0/2 (0%)	1/19 (5%)
Family Relationships	0/4 (0%)			2/3 (66%)					2/7 (29%)
Intimate Relationships	0/1 (0%)						0/1 (0%)		0/2 (0%)
Subdomain: Major Life Areas									0/10 (0%)
Major Life Areas	0/9 (0%)							0/1 (0%)	0/10 (0%)
Subdomain: Community, Social and Civic Life									7/26 (27%)
Community Life	0/2 (0%)	0/2 (0%)		1/1 (100%)					1/5 (20%)
Recreation and Leisure	0/8 (0%)	0/4 (0%)	1/1 (100%)	1/1 (100%)	4/6 (66%)			0/1 (0%)	6/21 (29%)
ICF Part E: Environmental Factors									
Subdomain: Products and Technology									15/30 (50%)
Products and Technology	0/1 (0%)	8/17 (47%)		2/3 (66%)	5/7 (71%)	0/1 (0%)		0/1 (0%)	15/30 (50%)
Subdomain: Natural Environment and Human-Made Changes to the Environment									3/10 (30%)
Natural Environment and Human-Made Changes to Environment		3/10 (30%)							3/10 (30%)
Subdomain: Support and Relationships									3/14 (21%)
Support and Relationships	0/8 (0%)			3/3 (100%)				0/3 (0%)	3/14 (21%)
Subdomain: Attitudes									0/2 (0%)
Attitudes	0/1 (0%)			0/1 (0%)					0/2 (0%)
Subdomain: Services, Systems and Policies									3/27 (11%)
Services, Systems and Policies	0/12 (0%)		2/3 (66%)	0/3 (0%)	1/1 (100%)			0/8 (0%)	3/27 (11%)

* Note: A total of n=366 question items were reviewed. Each question was assigned to subdomains in Part B, Part D and Part E as applicable.

1.1.1.1 Characteristics of Domain-Based Item Lists and Selection of Mobility Scales

Table V.3: Principle component factor list by WHO-ICF domain and subdomain

Factor List by Domain / Subdomain		
ICF Part B: Function		
Subdomain: Mental Function	Sleep Functions	F1 - Nighttime Awakening
Subdomain: Sensory Functions and Pain	Sensory Functions and Pain	F1 - Pain
Subdomain: Neuromusculoskeletal and Movement-Related Functions	PUL High Level: Shoulder Dimension	F1 - Unweighted or Range of Motion F2 - Weighted or Strength
	PUL Mid-Level: Elbow Dimension	F1 - Fine Motor and Reaching the Face F2 - Dressing F3 - Bimanual Strength Tasks
	PUL Distal-Level: Wrist and Finger Dimension	F1 - Hand Weakness F2 - Pointing F3 - Writing F4 - Holding Objects F5 - Email/Texting (Key Use)
	Complex: Standing from Seated	F1 - Standing from a Chair F2 - Standing from a Chair without Aid of Arms F3 - Standing from a Bathtub
	Complex: Transfers	F1 - Changing Positions in Bed F2 - Getting off the Toilet F3 - Wheelchair Transfers
	Trunk: Standing	F1 - Low to High Bending Reach F2 - Toilet and Sink Standing F3 - Bathing (Bath or Shower) F4 - Bathing (Shower Only)
	Trunk: Sitting	F1 - Bending at the Waist / Torso Control F2 - Torso Control - Toilet or Wheel Chair F3 - Unsupported Sitting with Time Element F4 - Unsupported Sitting F5 - Bathing Ability (Bathtub)
	LL: Running	F1-F3 - Sports Participation and Running (Not distinct factors)
	LL: Climbing	F1 - Long Duration or High Climbs F2 - Short Duration or Low Climbs
	LL: Walking	F1 - Long Duration Walks F2 - Short Walks and Uneven Surfaces F3 - Long Distance Walks (Ability to Do) F4 - Balance and Falls F5 - Long Distance Walks (Perception of Problem)
ICF Part D: Activities and Participation		
Subdomain: Learning and Applying Knowledge	Learning and Applying Knowledge	F1 - Missing School
Subdomain: Communication	Communication	F1 - Pointing and Manipulating Keyboards F2 - Writing F3 - Texting and Email (Behavioral Component)
Subdomain: Mobility	Changing and Maintaining Body Position	F1 - Transfers and Positional Changes F2 - Standing from Seated or Supine F3 - Sitting
	Carrying, Moving and Handling Objects	F1 - Tasks that Require Strength F2 - Tasks that Require Manual Dexterity F3 - Wheelchair-Related Manual Tasks
Subdomain: Self-Care	Washing Oneself	F1 - Washing, Drying in Bath or Shower F2 - Bathing, Bathtub Only F3 - Transfer to Bathtub
	Caring for Body Parts	F1 - Combing Hair, Brushing Teeth
	Toileting	F1 - Transferring to and From Toilet F2 - Self-Care on Toilet
	Dressing	F1 - Getting Dressed and Undressed F2 - Working Buttons and Zippers
Subdomain: Community, Social and Civic Life	Recreation and Leisure	F1-F3 Participation in Sports and Recreation (Not distinct factors)
ICF Part E: Environmental Factors		
Subdomain: Natural Environment and Human-Made Changes to the Environment	Natural Environment and Human-Made Changes to Environment	F1 - Ambulating Short Distances
Subdomain: Support and Relationships	Support and Relationships	F1 - Family Stress and Coping

Principle Components

Analysis: Following construction of the expert review-generated WHO-ICH-based responsive item lists, we examined each set of items using confirmatory principal components factor analysis in order to determine whether there were any potential underlying sub-constructs. A summary of factor analysis results is shown in Table V.3. Lists for sleep, pain, school function, caring for body parts, recreation and leisure, and family relationships all demonstrated an appreciable level of unidimensionality. However, most of the lists demonstrated multidimensionality even within groups of items that are frequently grouped together in clinical outcome measure tools. This suggests that even when question items are subdivided into categories according to the WHO-ICF model, there may be multiple underlying “pure” or latent constructs that could further elaborate on those subdivisions.

1.1.2 First Pass Rasch Analysis

We conducted a first-pass Rasch analysis of disease progression-responsive questions in each domain construct question

list. Specific analysis results are listed in Appendix V.1 (ICF Domain Construct Question List and Analyses) and results are summarized in Table V.4. Twenty-nine disease progression-responsive question lists were evaluated under the ICF Part B Structure and Function Domain. Twelve of 29 lists contained enough responsive items to conduct an initial Rasch

analysis, with 10 of the lists representing various neuromusculoskeletal and movement-related physical functions, 1 representing sensory functions and pain, and 1 representing sleep functions. Only three of those 12 lists demonstrated a somewhat acceptable person separation index of >0.7. and none of the lists covered an acceptable spectrum of disease severity from early ambulatory to late non-ambulatory patients. Twenty-three disease progression-responsive question lists were evaluated under the ICF Part D Activities and Participation Domain. Thirteen of 23 lists contained enough responsive items to conduct an initial Rasch Analysis. Of those 13 lists, 1 represented learning and applying knowledge, 1 represented communication, 3 represented mobility, 6 represented self care, 1 represented interpersonal interactions and relationships, and 1 represented recreation and leisure activities. Only the mobility domains demonstrated acceptable person-separation indices of 0.7-0.887, but question lists covered the spectrum of disease severity from early ambulatory to late non-ambulatory patients. Five disease progression-responsive question lists were evaluated under the ICF Part E Environmental Factors Domain. Three of 5 lists contained enough responsive items to conduct an initial Rasch analysis. Of those 3 lists, 1 represented use of products and technology, 1 represented the natural environment and man-made changes to the environment, and 1 represented support and relationships. None of the domains demonstrated acceptable person-separation indices.

Table V.4: Psychometric / Rasch analysis summary statistics for responsive item lists by domain/subdomain

Psychometric / Rasch Analysis Summary Statistics for Responsive Item Lists by Domain/Subdomain							
Domain/Subdomain	CFA # of Factors	Cronbach's Alpha	Item Fit	Person Fit	PSI (w/Extremes)	PSI (w/o Extremes)	Person/Item Separation Index
			Fit Residual (mean[SD])	Fit Residual (mean[SD])			
ICF Part B: Function							
Subdomain: Mental Function							
Intellectual Function	ND	ND	ND	ND	ND	ND	ND
Temperament and Personality Functions	ND	ND	ND	ND	ND	ND	ND
Energy and Drive Functions	ND	ND	ND	ND	ND	ND	ND
Sleep Functions	1	0.531	-4.6(2.7)	-0.32(0.76)	0.197	-0.332	0.278
Attention Functions	ND	ND	ND	ND	ND	ND	ND
Memory Functions	ND	ND	ND	ND	ND	ND	ND
Emotional Functions: Anxiety	ND	ND	ND	ND	ND	ND	ND
Emotional Functions: Depression	ND	ND	ND	ND	ND	ND	ND
Emotional Functions: Fear	ND	ND	ND	ND	ND	ND	ND
Emotional Functions: Frustration	ND	ND	ND	ND	ND	ND	ND
Emotional Functions: Satisfaction	ND	ND	ND	ND	ND	ND	ND
Subdomain: Sensory Functions and Pain							
Sensory Functions and Pain	1	0.51	-0.776	-0.71(0.82)	0.329	0.064	0.074
Subdomain: Functions of the Cardiovascular, Hematological, Immunological and Respiratory Systems							
Functions of the Hematological and Immunological Systems	ND	ND	ND	ND	ND	ND	ND
Functions of the Respiratory System	ND	ND	ND	ND	ND	ND	ND
Functions Related to the Digestive System	ND	ND	ND	ND	ND	ND	ND
Functions Related to Metabolism and the Endocrine System	ND	ND	ND	ND	ND	ND	ND
Subdomain: Neuromusculoskeletal and Movement-Related Functions							
PUL High Level: Shoulder Dimension	2	0.891	0.51(8.19)	-0.28(1.08)	0.793	0.761	0.767
PUL Mid-Level: Elbow Dimension	3	0.952	0.18(1.59)	-0.33(0.68)	0.713	0.583	0.586
PUL Distal-Level: Wrist and Finger Dimension	5	0.763	0.26(3.20)	-0.94(0.64)	-0.646	-0.472	-0.44
Complex: Standing from Supine	ND	0.849	0.73(0.61)	0.21(0.25)	0.760	0.760	0.859
Complex: Standing from Seated	3	0.755	-0.2(2.14)	-0.42(0.51)	-0.111	-3.972	-3.293
Complex: Transfers	3	0.970	0.48(2.8)	-0.71(0.91)	0.035	-2.230	-1.997
Head/Neck	ND	ND	ND	ND	ND	ND	ND
Trunk: Standing	4	0.935	1.04(1.35)	-0.30(1.28)	0.034	-0.685	-0.587
Trunk: Sitting	5	0.957	-0.97(2.56)	-0.37(0.71)	0.717	0.616	0.619
LL: Running	3	0.586	0.36(5.04)	-0.34(1.34)	0.490	0.578	0.581
LL: Climbing	2	0.953	-0.02(4.31)	-0.39(0.79)	0.772	0.689	0.691
LL: Walking	5	0.966	-0.93(5.46)	-0.30(1.21)	0.756	0.782	0.786
Subdomain: Functions of the Skin and Related Structures							
Functions of the Skin and Related Structures	ND	ND	ND	ND	ND	ND	ND
ICF Part D: Activities and Participation							
Subdomain: Learning and Applying Knowledge							
Learning and Applying Knowledge	1	0.691	-0.04(2.39)	-0.44(0.78)	0.561	0.415	0.421
Subdomain: General Tasks and Demands							
Undertaking Multiple Tasks	ND	ND	ND	ND	ND	ND	ND
Carrying Out a Daily Routine	ND	ND	ND	ND	ND	ND	ND
Handling Stress and Other Psychological Demands	ND	ND	ND	ND	ND	ND	ND
Subdomain: Communication							
Communication	3	0.125	0.02(3.58)	-0.40(0.26)	-1.068	-3.034	-2.93
Subdomain: Mobility							
Changing and Maintaining Body Position	3	0.986	-1.00(4.06)	-0.38(1.02)	0.848	0.848	0.850
Carrying, Moving and Handling Objects	3	0.956	0.42(5.22)	-0.29(1.11)	0.735	0.701	0.704
Walking and Moving	ND (highly collinear)	0.929	-1.65(6.70)	-0.58(1.28)	0.312	0.885	0.887
Moving Around Using Transportation	ND	ND	ND	ND	ND	ND	ND
Subdomain: Self-Care							
Washing Oneself	3	0.553	0.45(2.43)	-1.31(1.31)	-1.192	-2.535	-2.117
Caring for Body Parts	1	0.921	0.13(2.26)	-0.22(0.18)	-0.163	-3.068	-2.960
Toileting	2	0.915	-0.42(1.40)	-1.28(1.06)	0.558	0.234	0.277
Dressing	2	0.861	0.82(1.14)	-0.44(0.93)	0.535	-0.026	-0.008
Eating	ND	0.818	0.73(0.28)	-0.13(0.13)	-0.272	-1.99	-1.760
Drinking	ND	ND	ND	ND	ND	ND	ND
Looking After One's Health	ND	0.551	-0.38(2.35)	-0.28(0.73)	0.198	-0.333	-0.289
Subdomain: Domestic Life							
Domestic Life	ND	ND	ND	ND	ND	ND	ND
Subdomain: Interpersonal Interactions and Relationships							
Informal Social Relationships	ND	ND	ND	ND	ND	ND	ND
Family Relationships	ND	0.723	0.67(0.49)	-0.45(0.93)	0.359	0.305	0.345
Intimate Relationships	ND	ND	ND	ND	ND	ND	ND
Subdomain: Major Life Areas							
Major Life Areas	ND	ND	ND	ND	ND	ND	ND
Subdomain: Community, Social and Civic Life							
Community Life	ND	ND	ND	ND	ND	ND	ND
Recreation and Leisure	3	0.804	0.81(4.60)	-0.30(1.17)	0.501	0.448	0.454
ICF Part E: Environmental Factors							
Subdomain: Products and Technology							
Products and Technology	ND (highly collinear)	0.268	-0.06(3.55)	-0.60(1.13)	0.276	0.390	0.445
Subdomain: Natural Environment and Human-Made Changes to the Environment							
Natural Environment and Human-Made Changes to Environment	1	0.866	-0.05(0.64)	-0.22(0.37)	0.697	0.576	0.600
Subdomain: Support and Relationships							
Support and Relationships	1	0.799	0.36(1.31)	-0.45(1.19)	0.554	0.544	0.57
Subdomain: Attitudes							
Attitudes	ND	ND	ND	ND	ND	ND	ND
Subdomain: Services, Systems and Policies							
Services, Systems and Policies	ND	ND	ND	ND	ND	ND	ND

*Note: A total of 11-16 question items were reviewed. Each question was assigned to subdomains in Part B, Part D and Part E as applicable.

**ND = Not done due to having too few or no items unless otherwise noted.

1.1.3 Construct and Item Selection

Based on the first-pass Rasch analysis results, we selected the ICF Part D Activities and Participation Mobility domain question lists for further study and refinement using a second pass Rasch analysis. Selection of these subdomains, representing Walking and Moving, Changing and Maintaining Body Position, and Carrying, Moving and Handling Objects was not entirely unexpected because the initial responsive item evaluation was based on the concept of item change over time and with progressive loss of strength. In addition, the overall Activities and Participation Mobility construct represents multiple mobility functions across functional groups, where the Structure and Function neuromusculoskeletal and movement-related function-based lists focused tasks on specific affected parts of the body, thus limiting question set applicability to subpopulations where that function is still possible. The resulting questions comprise three domain-based item lists (Tables V.5 – V.7) reflecting a general latent construct of mobility, including functions of the upper extremities, trunk stability and lower extremities using person-reported question items representing crucial functions across the lifespan from early childhood to adulthood. The item lists included questions from the POSNA PODCI, PedsQL, PedsQL Neuromuscular Module and Neuro-QoL instruments. These items are questions with polytomous 1-4 or 1-5 Likert-type response ratings representing level of difficulty of performing a specific task (eg. climbing stairs).

Principle component analysis of the 3 item lists demonstrated multidimensionality in two. In the Changing and Maintaining Body Position question list, 3 factors suggested underlying functions associated with transfers and positional changes (Factor 1), standing from seated or supine (Factor 2), and unsupported sitting (Factor 3). In the Carrying, Moving and Handling Objects list, 3 factors suggested underlying functions associated with tasks that require strength (Factor 1), tasks that require manual dexterity (Factor 2), and a factor that may suggest manual tasks done in a wheelchair (Factor 3). Taken together the questions represent a range of function from near full function to significant impairment lacking the ability to walk and with minimal use of hands and reduced respiratory capacity.

Table V.5: Disease Progression-Responsive Item List for Walking and Moving

Instrument	Item Number / Question
NeuroQOL	1. I could keep my balance while walking for 30 minutes
NeuroQOL	4. I could walk for 15 minutes
NeuroQOL	5. I could walk between rooms
NeuroQOL	12. I could walk for 30 minutes
NeuroQOL	20. I fall down easily
NeuroQOL	21. I could walk on slightly uneven surfaces (such as cracked pavement)
NeuroQOL	22. I lose my balance easily
NeuroQOL	24. I could walk on rough, uneven surfaces (such as lawns, gravel driveway)
NeuroQOL	25. I could walk up and down ramps or hills
NeuroQOL	26. I could walk up and down curbs
NeuroQOL	31. I could walk across the room.
NeuroQOL	39. I could walk up 2-3 stairs
PedsQL	1. Walking more than one block
PedsQL	2. Running
POSNA PODCI	38. Run short distances?
POSNA PODCI	39. Bicycle or tricycle?
POSNA PODCI	40. Climb three flights of stairs?
POSNA PODCI	42. Walk more than a mile?
POSNA PODCI	43. Walk three blocks?
POSNA PODCI	44. Walk one block?
POSNA PODCI	34. How often does your child need help from another person for walking and climbing?
POSNA PODCI	52. How often did your child need help from another person for propelling a wheelchair outside on uneven surfaces such as grass, sidewalk or gravel?
POSNA PODCI	54. During the past one month, has it been easy or hard for your child to drive his power wheelchair or scooter by himself?

Table V.6: Disease Progression-Responsive Item List for Changing and Maintaining Body Position

Instrument	Item Number / Question
Factor 1: Transfers and Positional Changes	
NeuroQOL	4. I could move between my wheelchair and another seat such as a chair or bed
NeuroQOL	6. I could manage getting on and off the tub bench from a wheelchair
NeuroQOL	7. I could manage getting on and off the toilet from a wheelchair
NeuroQOL	10. I could get in and out of an adultsized chair
PedsQL NMM	16. It is hard to turn myself during the night.
NeuroQOL	16. I could keep my balance while walking for 15 minutes
NeuroQOL	19. I could turn my head all the way to the side to look at someone or something
NeuroQOL	21. I was able to cover my nose when sneezing
NeuroQOL	26. I was able to change positions in my bed.
POSNA PODCI	33. How often did your child use assistive devices (such as braces, crutches or a wheelchair) for walking or climbing?
POSNA PODCI	25. Stand while washing his hands and face at a sink?
POSNA PODCI	26. Sit in a regular chair without holding on?
POSNA PODCI	27. Get on and off a toilet or chair?
NeuroQOL	30. I was able to get out of bed by myself.
POSNA PODCI	28. Get in and out of bed?
NeuroQOL	31. I was able to get into bed by myself.
POSNA PODCI	31. How often did your child need help from another person for sitting and standing?
POSNA PODCI	32. How often did your child use assistive devices (such as braces, crutches or a wheelchair) for sitting and standing?
Factor 2: Standing from Seated or Supine	
NeuroQOL	2. I could get down on my knees without holding on to something.
NeuroQOL	8. I could stand up from an armless straight chair using my wheelchair
NeuroQOL	9. I could get on and off a low chair
NeuroQOL	11. I could get on and off a chair without using my arms.
NeuroQOL	13. I could get up from the floor by myself
NeuroQOL	17. I could stand on my tiptoes to reach for something
POSNA PODCI	30. Bend over from a standing position and pick up something off the floor?
NeuroQOL	33. I could bend over to pick something up.
Factor 3: Unsupported Sitting	
NeuroQOL	14. I could sit on a bench without support for 15 minutes
NeuroQOL	15. I could sit on a bench without back support for 30 minutes

Table V.7: Disease Progression-Responsive Item List for Carrying, Moving and Handling Objects

Instrument	Item Number / Question
Factor 1: Tasks that require strength	
POSNA PODCI	7. Lift heavy books?
POSNA PODCI	8. Pour a half gallon of milk?
POSNA PODCI	9. Open a jar that's been opened before?
PedsQL	4. Lifting something heavy
NeuroQOL	17. I was able to pick up a gallon of milk with one hand and set it on the table
NeuroQOL	33. I was able to open a jar by myself.
NeuroQOL	36. I was able to pull open heavy doors.
NeuroQOL	37. I was able to open the rings in school binders.
Factor 2: Tasks that require manual dexterity	
NeuroQOL	1. I was able to open small containers like snack bags or vitamins (regular screw top)
NeuroQOL	8. I was able to hold a full cup of water in my hand.
PedsQL NMM	8. My hands are weak.
PedsQL NMM	11. It is hard to use my hands.
NeuroQOL	12. I was able to use a knife to spread butter or jelly on bread
NeuroQOL	15. I was able to hold a plate full of food
NeuroQOL	19. I was able to cut a piece of paper in half with scissors
NeuroQOL	23. I was able to open a can of soda
POSNA PODCI	29. Turn doorknobs?
Factor 3: Manual tasks from a wheelchair.	
NeuroQOL	16. I could open a door that faced away from my wheelchair
NeuroQOL	17. I could open a door that was facing my wheelchair
NeuroQOL	19. I could manage the armrests on my wheelchair
NeuroQOL	20. I could manage the footrests on my wheelchair.

1.1.4 Rasch Analysis of the Activities and Participation Mobility Domain and Subdomains.

1.1.4.1 Walking and Moving

First Pass Analysis

In the first pass Rasch analysis, a person separation index of 0.88 demonstrated an excellent power of the overall model to individuate between respondents. Summary statistics showed that using all response items to model a "latent" construct of walking and moving ability across ambulatory and non-ambulatory stages of disease moderately over-discriminated, with a fit residual mean(SD) of -1.65(6.7), and a person fit residual mean(SD) of -0.58(1.28). The negative mean fit residual suggested that there was some degree of response dependency between items that required exploration. Review of individual item fit characteristics suggested that of the 23 items included in the model, 14 either contributed appreciably to model misfit (with an item residual $>|3.0|$), or showed non-random patterns in their variance (chi square p-values <0.01). Seven of the 23 items demonstrated ordered response thresholds. Results of first pass analyses are shown in detail in Appendix V.1 (ICF Domain Construct Question List and Analyses).

Item Rescoring: The first pass analysis revealed multiple items with disordered item response thresholds, indicating a lack of uniformity in the way individuals select question response choices, such as choices "with a little trouble" and "with some trouble", or "never" and "almost never", or "almost never" and "sometimes". For items such as these with overlapping response curves, we rescored the items to combine overlapping responses into a single score. Eighteen items were rescored. Following rescoring, items displayed ordered response thresholds, but also demonstrated high residuals indicating poor overall model fit. As a result, nine items were dropped, resulting in a final list of 15 items representing ambulatory functions. Changes to the question list and the response scoring structure are indicated in in Appendix V.1 (ICF Domain Construct Question List and Analyses).

Second-Pass Analysis

Model and Item Fit: Because the remaining questions all addressed ambulatory ability, analysis was restricted to individuals with ambulatory milestone scores only, and included 1,498 scorable responses and 139 extreme scores. In the second pass analysis, the person separation index at 0.88 continued to demonstrate very good power of the overall model to individuate between respondents. Summary statistics showed that using the selected subset of response items to model a construct of ambulatory ability still moderately over-discriminated, with a fit residual mean(SD) of -0.55(2.39), and a person fit residual mean(SD) of -0.36(0.98). The negative fit residual suggests that there is still a degree of response dependency that requires exploration. Fit statistics for the final model are displayed in Table V.8. Review of individual item fit (Table V.9) suggested that of the 15 items included in the model, 3 continue to contribute somewhat to model misfit (with an item residual $>|3.0|$).

Table V.8. Summary Test of Fit Statistics

Item Fit	Fit Residual Mean	SD
	-0.55	2.39
Person Fit	-0.36	0.98
Chi Squared Probability	1.0000	
Degrees of freedom	132	
Person Separation Index (PSI)	0.88	

Table V.9. Individual Item Fit for the 15 Items by item location (i.e. order of difficulty, most difficult to easiest). Items contributing to model Mis-fit items are shown in BOLD.

Seq	Item	Type	Location	SE	Residual	DF	ChiSq	DF	Prob	F-stat	DF1	DF2	Prob
5	Q5	Poly	-3.654	0.513	-0.158	38.43	1.758	8	0.987543
13	Q13	Poly	-1.342	0.256	-0.512	38.43	0.790	8	0.999258
18	Q18	Poly	-1.100	0.252	-0.423	38.43	0.429	8	0.999926
17	Q17	Poly	-1.065	0.047	-4.010	1236.51	7.130	9	0.623609
1	Q1	Poly	-0.675	0.296	0.070	37.60	1.377	9	0.997960
20	Q20	Poly	-0.114	0.306	0.465	37.60	1.364	9	0.998034
12	Q12	Poly	0.096	0.045	-2.884	1238.18	5.103	9	0.825255
23	Q23	Poly	0.164	0.303	-1.136	36.76	1.450	9	0.997499
4	Q4	Poly	0.208	0.301	-0.233	37.60	0.945	9	0.999554
19	Q19	Poly	0.507	0.328	0.319	37.60	1.997	9	0.991515
7	Q7	Poly	0.755	0.052	5.978	1247.37	6.757	9	0.662455
16	Q16	Poly	0.765	0.043	-4.618	1236.51	7.083	9	0.628463
6	Q6	Poly	1.522	0.338	-0.791	37.60	1.435	9	0.997598
9	Q9	Poly	1.837	0.046	-0.715	1243.19	2.725	9	0.974214
14	Q14	Poly	2.096	0.045	0.390	1243.19	3.516	9	0.940286

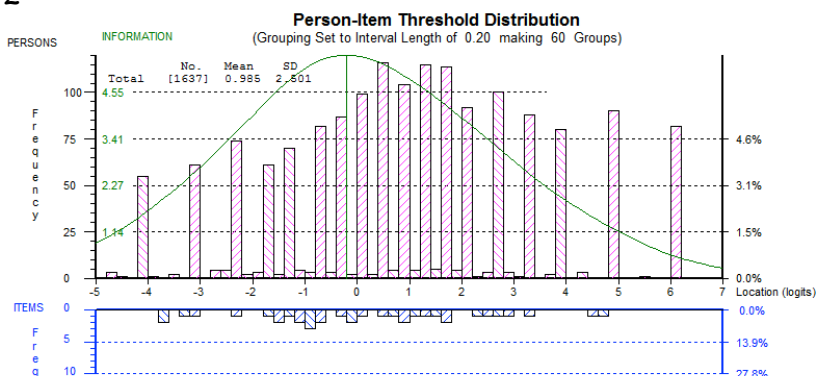
Individual Person Fit: Residuals values for person fit represent the difference between modelled responses and the individual's actual responses. Residual fit values $< |3.0|$ can be considered acceptable. Residuals for individual person fit ranged from -4.18 to 2.56 (mean -0.36, SD 0.98) indicating that overall, individuals in the sample fit the model well, with only 1 response (0.07%) falling outside the acceptable range.

Correlation of Residuals: Items in this domain-based list represent a latent construct of mobility in the context of a progressively debilitating disease measured using different representations (ie. standing, climbing, walking, breathing) of that mobility or lack thereof. Thus, we expect a moderate degree of covariation or dependency between variables, where a response on two items (ex. Ability to walk 1 block vs. Ability to walk 3 blocks) are both dependent on the underlying ability to walk long distances. For purposes of this analysis, we were willing to accept a moderate degree of correlation (ie. <0.4) between items. Items exceeding our acceptable limit of moderate residual correlation are shown in **Table V.10**. Of the items with moderately correlated residuals, only Question 13 and Question 18 seem to represent a similar function of walking on uneven surfaces. The remainder of the correlated items seem to represent items that are expected go together at different levels of function, most specifically items oriented toward walking distances versus climbing grades. Thus, we have selected to include these items in the model. It may be possible at some later point to condense these items into one or more questions with responses that capture a continuum of function, thus reducing or eliminating local dependency.

Table V.10. Local Dependency for Walking and Moving Scale Items

	Q1	Q4	Q9	Q12	Q13	Q16	Q17	Q18
Q12	-0.474	-0.499						
Q16	-0.417		-0.413	-0.458				
Q17					-0.781			
Q18					0.434	-0.400	-0.647	
Q19				-0.583				
Q20						-0.469	-0.495	
Q23					0.418	-0.524	-0.707	0.481

Person-Item Threshold Location: The person-item threshold distribution shown in **Figure V.3** reflects the overall distribution of the population examined (persons in pink), in this case children and adolescents with Duchenne muscular dystrophy, over a continuous logit scale. The individuals' position on the scale represents their overall level of function in a latent construct representation of ambulatory mobility as assessed using the selected set of person-reported response items from our Duchenne natural history study. The blue items then indicate the position of item thresholds, or points of change, between response categories for items included in the mobility domain list, and represent boundaries of the domain list's ability to readily differentiate between individuals at a given level of function. Points to the left indicate better function, points to the right indicate worse function. The distribution indicates that approximately 10% of respondents score to the right of the measurable scale (ie. ceiling effect), and slightly over 3% score to the left (ie. floor effect). This suggests that the current list does an acceptable job of assessing differences across a range of ambulatory individuals who are mildly affected to those who are on the verge of losing ambulation, but that it may lack the ability to evaluate individuals who are more severely affected. When evaluated by age group, mean(SD) scores for <4, 4-6, 7-9, 10-12, 13-15, 16-18 year old participants are statistically significantly different ($p=0.0000001$) at 2.1(1.26), 1.96(2.12), 1.43(2.35), 0.19(2.54), 0.21(2.63) and -0.65(1.75) respectively, in a pattern that overlaps but that is consistent with our understanding of disease progression with age in DMD. However, when evaluated according to clinically-measured functional milestones, those differences become more pronounced between individuals who are fully functional (Group 0), those who have lost the ability to stand from supine (Group 1), those who have in addition lost the ability to climb stairs (Group 2), and those who have subsequently lost the ability to rise from a chair but who remain ambulatory (Group 3). Group mean(SD) scores for those grades are statistically significantly different ($p=0.0000001$) at 1.65(2.27), -0.36(2.04), -1.84(1.67) and -2.35(1.56), respectively.

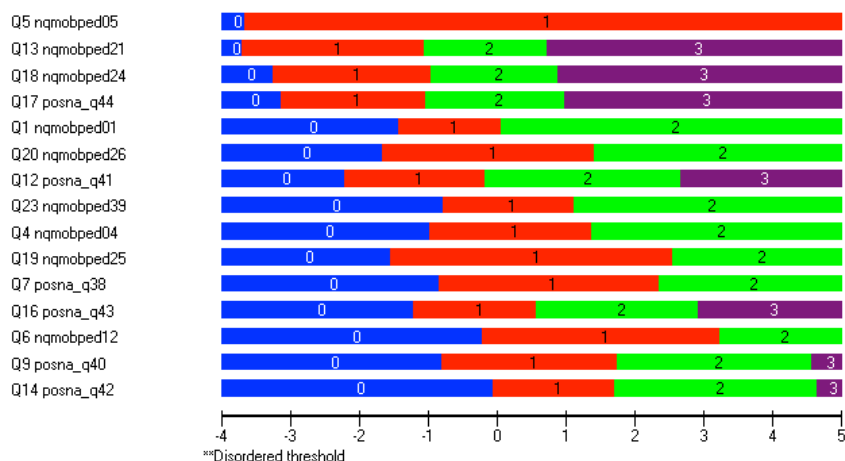
Figure V.3. Person-Item Threshold Distribution for the Walking and Moving Question Set

Threshold Ordering, Item Locations and Clinical “Face” Validity: Placing the questions in location order from easiest to most difficult yields the draft question set noted in **Table V.11**. The item location threshold map is presented as **Figure V.4**. Overall, these items represent a range of ambulatory mobility tasks that are progressively lost, starting with long distance and long duration walks and climbs, and running, followed by moderate distance and duration walks and climbs, followed by short walks, walks on uneven surfaces, and walking household distances. This is consistent with the clinical presentation and natural history of the disease and spans nearly the entire range of ambulatory function, suggesting that our construct has face validity as a representation of mobility.

Table V.11: Final Draft Walking and Moving Question Set

Q5	ngmobped05	I could walk between rooms
Q13	ngmobped21	I could walk on slightly uneven surfaces (such as cracked pavement)
Q18	ngmobped24	I could walk on rough, uneven surfaces (such as lawns, gravel driveway)
Q17	posna_q44	Walk one block?
Q1	ngmobped01	I could keep my balance while walking for 30 minutes
Q20	ngmobped26	I could walk up and down curbs
Q12	posna_q41	Climb one flight of stairs?
Q23	ngmobped39	I could walk up 2-3 stairs
Q4	ngmobped04	I could walk for 15 minutes
Q19	ngmobped25	I could walk up and down ramps or hills
Q7	posna_q38	Run short distances?
Q16	posna_q43	Walk three blocks?
Q6	ngmobped12	I could walk for 30 minutes
Q9	posna_q40	Climb three flights of stairs?
Q14	posna_q42	Walk more than a mile?

Figure V.4: Draft Walking and Moving Question Set Item Location Threshold Map.



1.1.4.2 Changing and Maintaining Body Position

First Pass Analysis

In the first pass analysis, a person separation index of 0.84 demonstrated an excellent power of the overall model to individuate between respondents. Summary statistics showed that using all response items to model a “latent” construct of trunk stability across ambulatory and non-ambulatory stages of disease moderately over-discriminated, with a fit residual mean(SD) of -1.00(4.06) and a person fit residual mean(SD) of -0.38(1.02). The negative mean fit residual suggested that there was some degree of response dependency between items that required exploration. Review of individual item fit characteristics suggested that of the 28

items included in the model, 9 either contributed appreciably to model fit or showed non-random patterns in their variance. Twelve of the 28 items demonstrated ordered response thresholds. Results of first pass analyses are shown in detail in Appendix V.1 (ICF Domain Construct Question List and Analyses).

Item Rescoring: The first pass analysis revealed multiple items with disordered item response thresholds, indicating a lack of uniformity in the way individuals select question response choices, such as choices "with a little trouble" and "with some trouble", or "never" and "almost never", or "almost never" and "sometimes". For items such as these with overlapping response curves, we rescored the items to combine overlapping responses into a single score. Sixteen items were rescored. Following rescoring, items displayed ordered response thresholds. All items were retained in the model, resulting in a final list of 28 items representing functions related to changing and maintaining body position. Changes to the response scoring structure are indicated in in Appendix V.1 (ICF Domain Construct Question List and Analyses).

Second Pass Analysis

Model and Item Fit: The questions presented in the list represent a range of functions that do not directly require the ability to ambulate, and thus the analysis included responses from all participants. Available data included 2,324 scorable responses and 927 extreme scores. In the second pass analysis, the person separation index at 0.86 continued to demonstrate very good power of the overall model to individuate between respondents. Summary statistics showed that using the selected subset of response items to model a construct of representing mobility during positional transfers still moderately over-discriminated, with a fit residual mean(SD) of -1.02(4.05), and a person fit residual mean(SD) of -0.45(1.29). The negative fit residual suggests that there is still a degree of response dependency that requires exploration. Fit statistics for the final model are displayed in Table V.12. Review of individual item fit (Table V.13) suggested that of the 28 items included in the model, 6 continue to contribute somewhat to model misfit (with an item residual $>|3.0|$).

Table V.12. Summary Test of Fit Statistics

Item Fit	Fit Residual Mean	SD
	-1.42	4.05
Person Fit	-0.45	1.29
Chi Squared Probability	0.999992	
Degrees of freedom	251	
Person Separation Index (PSI)	0.86	

Table V.13. Individual Item Fit for the 28 items. Items contributing to model mis-fit items are shown in BOLD.

Seq	Item	Type	Location	SE	FitResid	DF	ChiSq	DF	Prob
1	Q1	Poly	2.512	0.234	-1.069	82.03	0.644	9	0.999911
2	Q2	Poly	-0.601	0.175	2.309	72.32	3.437	9	0.944436
3	Q3	Poly	0.054	0.187	1.349	67.03	1.551	8	0.991836
4	Q4	Poly	-0.333	0.236	-1.836	68.80	1.473	9	0.997344
5	Q5	Poly	-0.113	0.231	0.672	68.80	0.950	9	0.999544
6	Q6	Poly	1.332	0.247	-1.411	82.91	0.803	9	0.999773
7	Q7	Poly	0.180	0.228	-1.174	82.03	1.379	9	0.997949
8	Q8	Poly	2.517	0.280	-0.980	82.91	0.781	9	0.999798
9	Q9	Poly	2.228	0.279	-0.518	82.03	1.117	9	0.999117
10	Q10	Poly	-0.903	0.171	1.668	85.55	2.434	9	0.982607
11	Q11	Poly	0.304	0.172	2.158	85.55	10.129	9	0.340126
12	Q12	Poly	-1.354	0.142	-1.130	239.02	1.090	9	0.999201
13	Q13	Poly	0.653	0.227	-1.795	82.03	0.940	9	0.999563
14	Q14	Poly	1.436	0.199	-1.238	82.03	1.096	9	0.999182
15	Q15	Poly	-3.518	0.169	0.022	88.20	1.543	9	0.996812
16	Q16	Poly	-3.047	0.207	-0.207	94.37	0.359	9	0.999993
17	Q17	Poly	-1.044	0.169	1.134	88.20	1.495	9	0.997186
18	Q18	Poly	-0.194	0.040	8.776	1991.56	13.183	9	0.154485
19	Q19	Poly	-0.379	0.040	-8.788	2003.03	17.583	9	0.040329
20	Q20	Poly	-1.840	0.043	4.278	2028.60	37.566	9	0.000021
21	Q21	Poly	0.266	0.041	-10.759	2021.55	21.876	9	0.009280
22	Q22	Poly	-0.304	0.171	-2.460	87.32	0.858	9	0.999702
23	Q23	Poly	-0.175	0.041	-10.698	2022.43	22.708	9	0.006887
24	Q24	Poly	-0.290	0.170	-2.313	85.55	0.906	9	0.999626
25	Q25	Poly	1.380	0.035	-5.266	2011.85	6.512	9	0.687816
26	Q26	Poly	1.522	0.206	-0.002	82.03	1.131	9	0.999071
27	Q27	Poly	0.168	0.041	0.297	2000.38	7.519	9	0.583239
28	Q28	Poly	-0.458	0.040	0.301	2003.91	4.464	9	0.878324

Individual Person Fit: Residuals values for person fit represent the difference between modelled responses and the individual's actual responses. Residual fit values $< |3.0|$ can be considered acceptable. Residuals for individual person fit ranged from -22.6 to 3.08 (mean -0.45, SD 1.29) indicating that overall, individuals in the sample fit the model moderately well, with 43 responses (1.8%) falling outside the acceptable range.

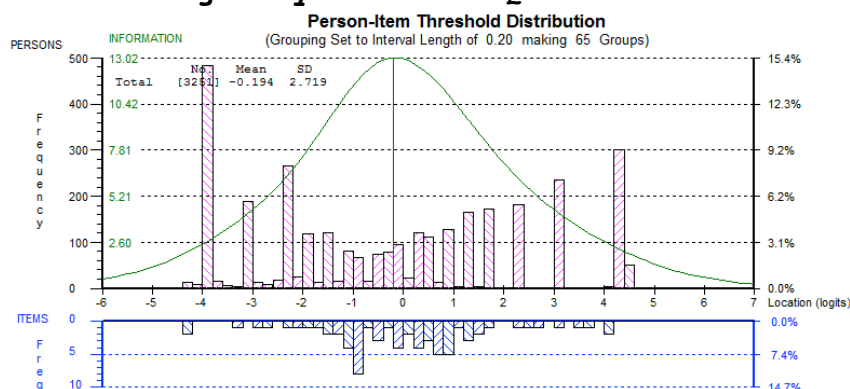
Correlation of Residuals: As noted previously, for purposes of this analysis we were willing to accept a moderate degree of correlation (ie. < 0.4) between items. Items exceeding our acceptable limit of moderate residual correlation are shown in **Table V.14**. Q1 is getting down on knees without holding on to something. This correlates moderately with getting out of chairs, getting up from the floor, and use of assistive devices. Q4 is getting on/off a toilet from a wheelchair, which correlates with Q11 sitting on a bench without back support for >30 minutes. Q10 is sitting on a bench for >15 minutes, which correlates with sitting on a bench for >30 minutes, and getting out of bed. Q19 is standing at a sink, which correlates with getting into bed. Q22 is getting out of bed, which correlates with Q24 getting into bed, and Q23 getting into and out of bed. In similar fashion, Q23 and Q24 are correlated. Q24 getting into bed also correlates moderately with bending over to pick something up. It is clear that many of these items constitute questions regarding similar functions. However, the similar function items are often from different instruments (ie. PODCI versus NeuroQoL) which were not uniformly administered across the participant age groups, because NeuroQoL items were added to a more recent version of the protocol. Thus, dropping one item in favour of the other results in significant reduction in the overall sample available for analysis. Thus, we have elected to include these items in the model. However, it will be necessary during further instrument validation to condense these items into one or more questions that can be uniformly administered to future study populations.

Table V.14. Local Dependency for Changing and Maintaining Body Position Scale Items

	Q1	Q4	Q10	Q19	Q22	Q23	Q24
Q6	0.560						
Q8	0.412						
Q9	0.443						
Q11		0.416	0.492				
Q18	-0.471						
Q22			-0.431				
Q23					0.460		
Q24				0.519	0.780	0.451	
Q26							-0.42
Q28	-0.457						

Person-Item Threshold Location: The person-item threshold distribution shown in **Figure V.5** reflects the overall distribution of the population examined (persons in pink), in this case individuals with Duchenne muscular dystrophy, over a continuous logit scale. The distribution indicates that approximately 12% of respondents score to the right of the measurable scale (ie. ceiling effect), and slightly over 18% score to the left (ie. floor effect). This suggests that the current list does an acceptable job of assessing differences across a range of ambulatory and non-ambulatory individuals from those who are ambulatory and moderately affected to those who have lost ambulation but still retain some ability to sit unsupported. When evaluated by age group, mean(SD) scores for <4, 4-6, 7-9, 10-12, 13-15, and 16-18 year old participants are statistically significantly different ($p=0.0000001$) at 3.6(1.32), 2.76(1.43), 1.98(1.91), -0.54(2.47), -1.56(2.27) and -2.17(1.83) respectively, in a pattern that overlaps but that is consistent with our understanding of disease progression with age in DMD. When evaluated according to clinically-measured functional milestones across the entire disease severity spectrum, those differences remain pronounced between individuals who are fully functional (Group 0), those who have lost the ability to stand from supine (Group 1), those who have in addition lost the ability to climb stairs (Group 2), those who have subsequently lost the ability to rise from a chair but who remain ambulatory (Group 3), those who have lost the ability to walk but who can bring their hand to their mouth (Group 4), those who have lost the ability to bring their hand to their mouth (Group 5), and those who cannot bring their hand to their mouth and have a forced vital capacity <30% predicted (Group 6). Group mean(SD) scores for those groups are statistically significantly different ($p=0.0000001$) at 2.52(1.49), 1.01(1.21), 0.25(0.84), -0.49(0.85), -2.28(1.30), -2.92(1.17) and -3.01(1.16), respectively.

Figure V.5. Person-Item Threshold Distribution for the Changing and Maintaining Body Position Question Set

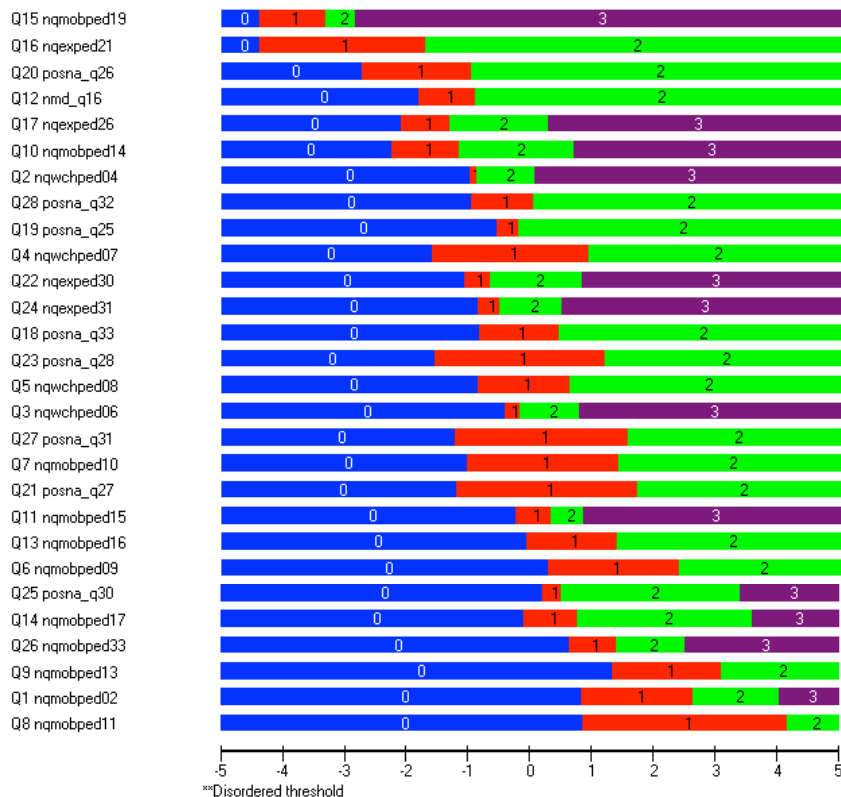


Threshold Ordering, Item Locations and Clinical "Face" Validity: Placing the questions in location order from easiest to most difficult yields the draft question set noted in **Table V.15**. The item location threshold map is presented as **Figure V.6**. Overall, these items represent a range of positional change and transfer abilities that are progressively lost, starting with standing from a chair without use of the arms, followed by bending to pick items off of the floor, followed by self-transfer to a chair, toilet or bed using the arms, followed by changing positions in bed, followed by ability to turn the head. This is consistent with the clinical presentation and natural history of the disease and spans a large range of function, suggesting that our construct has face validity as a representation of transfer and positional change mobility. Referring to the apparent latent factors identified in the principle component analysis, items aligning with the second factor (standing from seated or supine) predominate in the stronger end of the spectrum, while items aligning with the first factor (transfers and positional changes) predominate in the weaker 2/3 of the scale. Tasks associated with the third factor (unsupported sitting) end up in the middle and probably represent a short period of time where individuals are wheelchair users but still have some ability to maintain seated balance and trunk posture. As discussed previously, several of these questions from different instruments used in different sub-populations duplicate similar activities and align in similar fashion with respect to order of difficulty. Those questions could be condensed into single items and re-tested.

Table V.15: Final Draft Changing and Maintaining Body Position Question Set

Q15	nqmobped19	I could turn my head all the way to the side to look at someone or something
Q16	ngexped21	I was able to cover my nose when sneezing
Q20	posna_q26	Sit in a regular chair without holding on?
Q12	nmd_q16	It is hard to turn myself during the night.
Q17	ngexped26	I was able to change positions in my bed
Q10	nqmobped14	I could sit on a bench without support for 15 minutes
Q2	nqwchped04	I could move between my wheelchair and another seat such as a chair or bed
Q28	posna_q32	How often did your child use assistive devices (such as braces, crutches or a wheelchair) for sitting and standing?
Q19	posna_q25	Stand while washing his hands and face at a sink?
Q4	nqwchped07	I could manage getting on and off the toilet from a wheelchair
Q22	ngexped30	I was able to get out of bed by myself.
Q24	ngexped31	I was able to get into bed by myself.
Q18	posna_q33	How often did your child use assistive devices (such as braces, crutches or a wheelchair) for walking or climbing?
Q23	posna_q28	Get in and out of bed?
Q5	nqwchped08	I could stand up from an armless straight chair using my wheelchair
Q3	nqwchped06	I could manage getting on and off the tub bench from a wheelchair
Q27	posna_q31	How often did your child need help from another person for sitting and standing?
Q7	nqmobped10	I could get in and out of an adultsized chair
Q21	posna_q27	Get on and off a toilet or chair?
Q11	nqmobped15	I could sit on a bench without back support for 30 minutes
Q13	nqmobped16	I could keep my balance while walking for 15 minutes
Q6	nqmobped09	I could get on and off a low chair
Q25	posna_q30	Bend over from a standing position and pick up something off the floor?
Q14	nqmobped17	I could stand on my tiptoes to reach for something
Q26	nqmobped33	I could bend over to pick something up.
Q9	nqmobped13	I could get up from the floor by myself
Q1	nqmobped02	I could get down on my knees without holding on to something.
Q8	nqmobped11	I could get on and off a chair without using my arms.

Figure V.6: Draft Changing and Maintaining Body Position Question Set Item Location Threshold Map.



1.1.4.3 Carrying, Moving and Handling Objects

First Pass Analysis

In the first pass analysis, a person separation index of 0.73 demonstrated acceptable power of the overall model to individuate between respondents. Summary statistics showed that using all response items to model a "latent" construct of upper extremity ability across ambulatory and non-ambulatory stages of disease discriminates moderately well, with a fit residual mean(SD) of 0.42(5.21) and a person fit residual mean(SD) of -0.29(1.10). Review of individual item fit characteristics suggested that of the 21 items included in the model, 5 either contributed appreciably to model fit or showed non-random patterns in their variance. Nine of the 21 items demonstrated ordered response thresholds. Results of the first pass analysis are shown in detail in Appendix V.1 (ICF Domain Construct Question List and Analyses).

Item Rescoring: The first pass analysis revealed multiple items with disordered item response thresholds, indicating a lack of uniformity in the way individuals select question response choices, such as choices "with a little trouble" and "with some trouble", or "never" and "almost never", or "almost never" and "sometimes". For items such as these with overlapping response curves, we rescored the items to combine overlapping responses into a single score. Twelve items were rescored. Following rescoring, items displayed ordered response thresholds. All items were retained in the model, resulting in a final list of 21 items representing functions related to carrying, moving and handling objects. Changes to the response scoring structure are indicated in in Appendix V.1 (ICF Domain Construct Question List and Analyses).

Second Pass Analysis

Model and Item Fit: The questions presented in the list represent a range of functions that do not directly require the ability to ambulate, and thus the analysis included responses from all participants. Available data included 2,908 scorable responses and 672 extreme scores. In the second pass analysis, the person separation index at 0.75 continued to demonstrate acceptable power of the overall model to individuate between respondents. Summary statistics showed that using the selected subset of response items to model a construct of representing manual mobility still discriminates moderately well, with a fit residual mean(SD) of 0.14(4.96), and a person fit residual mean(SD) of -0.32(1.06). Fit statistics for the final model are displayed in Table V.16. Review of individual item fit (Table V.17) suggested that of the 21 items included in the model, 3 continue to contribute somewhat to model misfit (with an item residual $>|3.0|$).

Table V.16. Summary Test of Fit Statistics

Item Fit	Fit Residual Mean	SD
	0.14	4.96
Person Fit	-0.32	1.06
Chi Squared Probability	1.00	
Degrees of freedom	189	
Person Separation Index (PSI)	0.75	

Table V.17. Individual Item Fit for the 21 items. Items contributing to model mis-fit are shown in BOLD.

Seq	Item	Type	Location	SE	FitResid	DF	ChiSq	DF	Prob
1	Q1	Poly	0.875	0.027	-7.290	2364.62	11.953	9	0.215950
2	Q2	Poly	-0.578	0.130	0.797	86.55	0.847	9	0.999716
3	Q3	Poly	0.717	0.025	-9.572	2360.54	15.537	9	0.077204
4	Q4	Poly	-0.130	0.026	-0.188	2356.46	4.659	9	0.862926
5	Q5	Poly	0.774	0.033	18.034	2163.76	47.962	9	0.000000
6	Q6	Poly	-1.225	0.178	0.414	84.92	2.055	9	0.990567
7	Q7	Poly	-0.368	0.101	1.197	255.57	0.614	9	0.999927
8	Q8	Poly	-1.341	0.114	0.397	253.12	0.705	9	0.999868
9	Q9	Poly	-0.893	0.181	-0.244	86.55	0.894	9	0.999645
10	Q10	Poly	0.215	0.136	0.443	82.47	1.073	9	0.999250
11	Q11	Poly	0.084	0.187	1.258	68.59	1.777	9	0.994518
12	Q12	Poly	0.093	0.145	0.378	69.40	0.469	9	0.999977
13	Q13	Poly	1.975	0.220	-1.292	80.02	0.911	9	0.999617
14	Q14	Poly	-0.784	0.169	-0.211	71.04	0.822	9	0.999749
15	Q15	Poly	-1.093	0.135	2.561	86.55	1.661	9	0.995764
16	Q16	Poly	-0.231	0.185	1.798	69.40	0.668	9	0.999895
17	Q17	Poly	0.030	0.178	-0.187	82.47	0.925	9	0.999592
18	Q18	Poly	-0.887	0.035	-1.436	2298.48	10.752	9	0.293093
19	Q19	Poly	0.868	0.150	-0.974	81.65	0.573	9	0.999945
20	Q20	Poly	1.791	0.213	-1.309	80.83	1.009	9	0.999416

Individual Person Fit: Residuals values for person fit represent the difference between modelled responses and the individual's actual responses. Residual fit values $< |3.0|$ can be considered acceptable. Residuals for individual person fit ranged from -10.6 to 2.86 (mean -0.32, SD 1.06) indicating that overall, individuals in the sample fit the model moderately well, with only 8 responses (0.27%) falling outside the acceptable range.

Correlation of Residuals: As noted previously, for purposes of this analysis we were willing to accept a moderate degree of correlation (ie. <0.4) between items. Items exceeding our acceptable limit of moderate residual correlation are shown in **Table V.18**. Q3 is opening a gallon of milk, which correlates with opening heavy doors. Q5 is lifting something heavy, which correlates with Q14 using scissors, Q17 opening a can of soda and Q21 opening rings on school binders. Q14 using scissors also

correlates with Q16, managing footrests on a wheelchair. Taken together, the items represent different activities, although the use of scissors, opening a soda can and opening school binders are activities that require maintenance of manual dexterity but also a moderate degree of finger strength. Because the correlation between these activities is and lifting heavy objects is negative, it is likely that these items represent a continuum of strength-related activities. However, as they represent different levels of strength we have elected to include them all in the model. It may be necessary at some point to condense these items into a smaller number of questions or a single question representing strength.

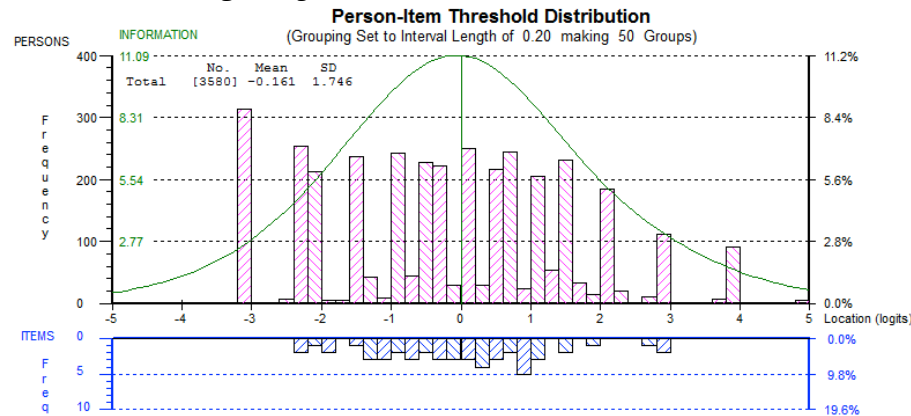
Table V.18. Local Dependency for the Carrying, Moving and Handling Objects Scale Items

	Q3	Q5	Q14
Q14		-0.428	
Q16			0.406
Q17		-0.405	
Q20	0.432		
Q21		0.518	

Person-Item Threshold Location: The person-item threshold distribution shown in **Figure V.7** reflects the overall distribution of the population examined (persons in pink), in this case individuals with Duchenne muscular dystrophy, over a continuous logit scale. The distribution indicates that approximately 5% of respondents score to the right of the measurable scale (ie. ceiling effect), and slightly over 13% score to the left (ie. floor effect). This suggests that the current list does an acceptable job of assessing differences across a range of ambulatory and non-ambulatory individuals from those who are ambulatory and mildly to moderately affected to those who have lost ambulation but still retain some moderate degree of hand function to perform small manual tasks that do not require strength. When evaluated by age group, mean(SD) scores for <4, 4-6, 7-9, 10-12, 13-15, 16-18 and >18 year old participants are statistically significantly different ($p=0.0000001$) at 0.39(0.72), 1.03(1.46), 0.90(1.38), -0.07(1.63), -0.49(1.69), -0.94(1.66) and -1.45(1.27), respectively, in a pattern that overlaps but that is consistent with our understanding of disease progression with age in DMD. It is important to point out the slightly lower score for children under 4 years of age relative to children from 4-9 years old, and for whom it would be developmentally normal to require assistance in many of the represented tasks. When evaluated according to clinically-measured functional milestones across the entire disease severity spectrum, those differences remain pronounced between individuals who are fully functional (Group 0), those who have lost the ability to stand from supine (Group 1), those who have in addition lost the ability to climb stairs (Group 2), those who have subsequently lost the ability to rise from a chair but who remain ambulatory (Group 3), those who have lost the ability to walk but who can bring their hand to their mouth (Group 4), those who have lost the ability to bring their hand to their mouth (Group 5), and those who cannot bring their hand to their mouth and have a forced vital capacity <30% predicted (Group 6). Group mean(SD) scores for those groups are statistically significantly different ($p=0.0000001$) at 1.15(1.35), 0.84(1.27), 0.24(1.09), 0.02(1.20), -0.63(1.34), -1.69(1.19) and -2.10(0.76), respectively. It should be noted that while this domain does not perform well in young children whose developmental abilities are still

growing, it is the only one to demonstrate an appreciable point difference between late stage individuals who are only subdivided according to respiratory function differences.

Figure V.7. Person-Item Threshold Distribution for the Carrying, Moving and Handling Objects Question Set

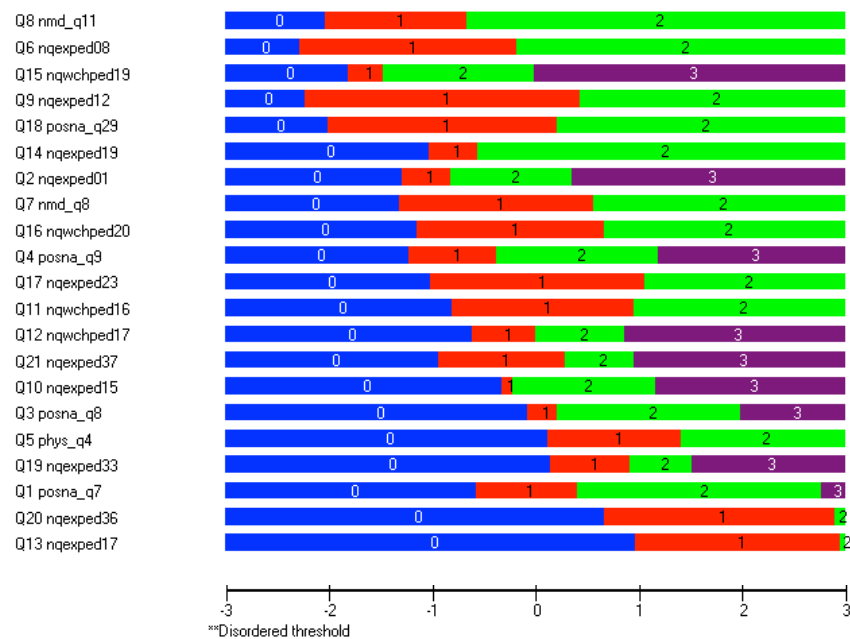


Threshold Ordering, Item Locations and Clinical "Face" Validity: Placing the questions in location order from easiest to most difficult yields the draft question set noted in **Table V.19**. The item location threshold map is presented as **Figure V.8**. Overall, these items represent a range of manual abilities that are progressively lost, starting with lifting and moving heavy objects such as heavy books, a half gallon of milk and heavy doors, followed by manual tasks such as opening school binders or soda cans or opening doors from a wheelchair, followed by opening small containers or using scissors, followed by using utensils or holding a cup. This is consistent with the clinical presentation and natural history of the disease and spans a large range of function, suggesting that our construct has face validity as a representation of manual abilities. Referring again to the apparent latent factors identified in the principle component analysis, items aligning with the first factor (tasks that require strength) predominate in the stronger end of the spectrum, while items from the second factor (tasks that require manual dexterity) predominate in the weaker end of the spectrum. Tasks associated with the third factor (tasks from a wheelchair) end up in the middle and probably represent a short period of time where individuals are wheelchair users but still have some functional degree of shoulder and elbow use. Given that the question set still demonstrates a floor effect for a portion of the population, there is a clear need for adoption of additional questions that address fine motor and hand functions such as writing ability or keyboard use.

Table V.19: Final Draft Carrying, Moving and Handling Objects Question Set

Q8	nmd_q11	It is hard to use my hands.
Q6	nquexped08	I was able to hold a full cup of water in my hand.
Q15	nqwchped19	I could manage the armrests on my wheelchair
Q9	nquexped12	I was able to use a knife to spread butter or jelly on bread
Q18	posna_q29	Turn doorknobs?
Q14	nquexped19	I was able to cut a piece of paper in half with scissors
Q2	nquexped01	I was able to open small containers like snack bags or vitamins (regular screw top)
Q7	nmd_q8	My hands are weak.
Q16	nqwchped20	I could manage the footrests on my wheelchair.
Q4	posna_q9	Open a jar that's been opened before?
Q17	nquexped23	I was able to open a can of soda
Q11	nqwchped16	I could open a door that faced away from my wheelchair
Q12	nqwchped17	I could open a door that was facing my wheelchair
Q21	nquexped37	I was able to open the rings in school binders.
Q10	nquexped15	I was able to hold a plate full of food
Q3	posna_q8	Pour a half gallon of milk?
Q5	phys_q4	Lifting something heavy
Q19	nquexped33	I was able to open a jar by myself.
Q1	posna_q7	Lift heavy books?
Q20	nquexped36	I was able to pull open heavy doors.
Q13	nquexped17	I was able to pick up a gallon of milk with one hand and set it on the table

Figure V.8: Draft Carrying, Moving and Handling Objects Question Set Item Location Threshold Map.



Discussion

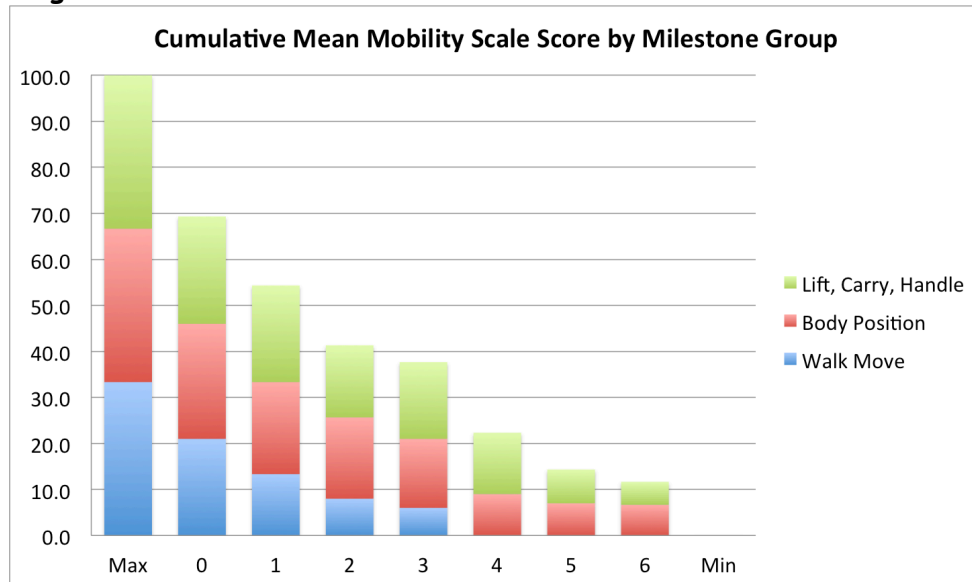
The initial results of our evaluation of sensitivity to disease milestones and one-year change yielded a list of items that spans multiple domains within the WHO-ICF framework. Few items exist, however, that represent functions that are unrelated to neuromusculoskeletal function and movement. Certainly, the devices we selected in the Duchenne Natural History Study (DNHS) have previously demonstrated deficits among DMD patients relative to typically developing controls and other groups in non mobility-related domains such as life satisfaction, but our results suggest that, at least between contiguous milestone classification groups or over relatively short one-year periods of time, those deficits remain somewhat fixed. That those more psychosocial-oriented items failed to show differences or changes is not entirely unexpected, and there are

likely to be classification schemes other than disease milestones where those items might demonstrate change over time.

Subsequently, we focus on a set of items that have demonstrated sensitivity to disease and one-year change which correspond to the mobility subdomain domain of the WHO-ICH Activities and Participation domain and describe arm, leg and trunk functions that are progressively lost during the course of Duchenne muscular dystrophy. We have demonstrated that despite the continuing existence of ceiling and floor effects in each of the three person-reported mobility-oriented domain scores discussed above, they describe a continuum of individuals with Duchenne muscular dystrophy across most of the currently observed range of ages and stages of disease who we have profiled in the DNHS (Henricson, Abresch et al. 2013, McDonald, Henricson et al. 2013). Furthermore, taken together, the scales provide a patient (or patient proxy)-assessed range of functional ability of the arms, legs and trunk that ranges from newly diagnosed and nearly typical-appearing young children to severely impaired young adults at the end of their expected life span. Through the Rasch analysis approach and comparison with previously described functional milestones that are progressively and predictably lost as the disease progresses, we have demonstrated the initial psychometric characteristics and clinical validity of each scale, and provided initial estimates of mean linearized mobility domain scores for each functional milestone group.

While each of the mobility domain scores may be useful in its own right, the power of this approach is in the development of a combined and linear mobility score that can be used across the entire range of functional abilities associated with the disease. Figure V.9 below provides a look at one potential method of achieving this such a combined score. By converting each of the three mobility domain logit location ranges to a simple 0-100 point scale (with 100 representing best function and 0 representing worst), we are able to then combine all three scores to create an average mobility score for each milestone group. As depicted below then, individuals at near full function in Milestone Group 0 have average score of 70 points, with each mobility domain contributing approximately 1/3 of the total score. As milestones are progressively lost, we see that on average the functions described in the Walking and Moving domain are lost first, followed by a gradual and somewhat proportional loss of the Maintaining Body Position and Carrying, Moving and Handling Objects domain functions.

Figure V.9M



1.1.1.5 Revisions to Question Syntax and the Response Structure

While this combined scale initially appears to possess the desirable qualities of being a continuous assessment scale that can be used across the entire span of ages and stages of the disease, the three domains still have mis-fitting items and ceiling and floor effects that could be optimized through revisions to the question set, but with respect to item content and presentation. First, it appears that overall, the items derived from the PODCI device continue to yield high fit residuals, suggesting that there may be a moderate degree of subjectivity in the way that patients select their responses. In comparison, items from the NeuroQOL devices more frequently demonstrate acceptable fit residuals, suggesting that they are answered in a much more predictable pattern as the disease progresses. We have previously noted that the lack of responsiveness of the PedsQL relative to 6-minute walk velocity may be due in part to the wording of the questions such that they ask "In the past 7 days, *how much of a problem* has it been for you to..." (responses Never, Almost Never, Sometimes, Often, Almost Always), while the more responsive PODCI instrument asks questions in the manner of "During the last week, has it been easy or hard for you to..." (responses Easy, A Little Hard, Very Hard, Can't Do) (Henricson, Abresch et al. 2013). While this is a subtle difference, the former adds a subjective aspect of whether an activity is desirable in addition to it's level of difficulty, while the PODCI items simply ask about overall difficulty. Here with respect to the PODCI versus the NeuroQOL, we may be seeing a similar effect. Items from the NeuroQOL scales underwent extensive testing, response revision and cognitive debriefing prior to publication using the syntax "In the past 7 days, I could _____ (responses With no trouble, With a little trouble, With some trouble, With a lot of trouble". It is apparent from our rescoring efforts to correct disordered response thresholds on many of our items that there is still some inconsistency in differentiating between "With a little trouble" and "With some trouble", and this question style lacks a "can't do at all" response, but it may be appropriate to revise the questions to reflect a combination of PODCI and NeuroQOL styles, with

a syntax that reads: In the past 7 days, I could _____ (responses With no trouble, With some trouble, With a lot of trouble, Can't do).

In addition to revision of individual question presentation, our mixed use of instruments across different ages has resulted in the retention of multiple items that are from different instruments but that relate to the same overall concept. For instance, use of the PODCI and NeuroQOL in different groups has given us one question about getting in and out of bed, one question about getting into bed, and one question about getting out of bed. These items, naturally, are highly co-dependent, and ideally only one would be left in the final model. Further Rasch analysis following a uniform application of these questions to an entire (planned) future cohort will allow us to simplify the model even more.

A third type of question adjustment that we can approach will be consolidation of questions regarding similar tasks at different levels of difficulty. For instance, the NeuroQOL question "I was able to open a jar by myself" and the PODCI item "Open a jar that's been opened before" represent similar functions and load on the same factor according to principle component analysis, but the latter aligns further down the scale with easier items relative to the former. We may be able to use the factor loadings and question content as a guide to combine questions with a syntax similar to:

In the past 7 days, I could open a jar if:

- 1) Easily, even if it had never been opened
- 2) Easily, if it had been opened before
- 3) With some difficulty, if it had been opened before
- 4) With a lot of difficulty, if it had been opened before
- 5) Can't do

1.1.6 Comparable instruments from clinical practice: The North Star Ambulatory Assessment, Egen Klassifikation Scale, and Performance of the Upper Limb (PUL) Assessment.

Another issue with the domain item lists as presented at this point is the continued existence of ceiling and floor effects in all three mobility domains. In the Walking and Moving item list, questions represent a wide range from difficult (walking more than a mile) to easy (walking between rooms). In the Changing and Maintaining Body Position list, tasks range from difficult (getting out of a chair without using one's arms) to easy (moving one's head to look to the side). In the Carrying, Moving and Handling Objects list, tasks range from difficult (picking up a gallon of milk) to easy (holding a cup of water). However, we can readily develop candidate items on the more difficult and easier ends of these scales by referring to some of the analogous validated functional clinical examinations that are currently in use. The North Star Ambulatory Assessment (NSAA) contents are similar to those from the Walking and Moving item list; the Egen Klassifikation (EK) Scale is similar in content to the Changing and Maintaining Body Position list; and the Performance of the Upper Limb (PUL) Assessment is similar to the Carrying, Moving and Handling Objects list.

Both the NSAA and the PUL were developed using Rasch techniques for construction and validation tools (Mayhew, Cano et al. 2011, Mayhew, Mazzone et al. 2013). Mayhew and colleagues collected cross-sectional NSAA assessment data from the North Star database for 191 ambulatory boys

with DMD between 3-15 years of age and examined properties of the instrument that included clinical meaningfulness, appropriateness of item targeting, order of item response categories, Rasch model fit, and instrument reliability and stability. A copy of the NSAA device is attached for reference as Appendix V.2. They determined that Rasch analysis upheld reliability and validity of the instrument as a measure of mobility and ambulatory function in DMD that logically follows functional loss resulting from disease progression. Furthermore, they described an s-shaped logistic curve relationship for a transformation scale between raw scores and logit-based location on the continuous Rasch-based scale. That function illustrated that raw scale scores yield different continuous interval score changes over the possible range of instrument, with continuous score changes that are magnified at both tails of the distribution relative to the middle. In a longitudinal follow up paper, Mayhew used a similar cohort of 198 DMD patients between 4 and 18 years of age from the North Star database to examine NSAA responsiveness to disease progression over time and minimal clinically-important difference (MCID) of mean scores for GC-treated and GC-naïve patients (Mayhew, Cano et al. 2013). They also reported a 0-100 point logit transformed scale relative to the 0-32-point NSAA raw score scale. In both GC-treated and GC-naïve patients, they showed the instrument is responsive to previously described improvements in ambulatory ability scores for children under 7 due to milestone attainment during the early childhood growth spurt (Mazzone, Martinelli et al. 2010, Henricson, Abresch et al. 2012), as well as functional loss due to disease progression over the range of individuals in the sample. Importantly, they also demonstrated that by linearizing items on the Rasch model scale, distribution-based minimal clinically important differences in score across the range of function can be directly linked to loss of specific functional abilities. The authors illustrated this by demonstrating that a change from a score of 50 to 40 on the transformed scale directly corresponds to loss of ability to rise from the floor without assistance.

The EK scale was developed by the Danish muscular dystrophy association as a clinical tool to assess overall functional ability in the non-ambulatory DMD population (Steffensen, Hyde et al. 2001, Steffensen, Lyager et al. 2002). This tool includes assessments comprised of functional assessments measuring interaction of physical components such as muscle strength, range of motion, respiratory status, wheelchair dependence and age. The Scale assesses ten functional categories (EK 1-10), each contributing to an overall picture of function. A copy of the EK Scale device is attached for reference as Appendix V.3

Mayhew et al also developed the upper limb assessment tool called the Performance of the Upper Limb module for Duchenne muscular dystrophy (Mayhew, Mazzone et al. 2013). A copy of the PUL device is attached for reference as Appendix V.4. The device was developed using upper limb functional performance items from the Brooke upper extremity functional scale (Brooke, Griggs et al. 1981), the Jebsen-Taylor Hand Function Test (JTHFT) (Jebsen, Taylor et al. 1969) and the Motor Function Measure (MFM) (Berard, Payan et al. 2006) selected on the basis of a conceptual framework that items should provide assessment of upper limb and hand mobility including impact of weakness, growth and development of joint contractures across both ambulatory and non-ambulatory phases of disease. Item selection by a key informant workgroup of clinicians occurred following assessment using the full instrument measures performed on 61

volunteers with DMD 11-30 years of age. The resulting item list was then assessed in 86 volunteers with DMD between 5-27 years of age. Rasch analysis of the pilot instrument data demonstrated excellent item fit and good reliability, with some collapsing of disordered item responses into broader but clinically appropriate categories. Development of the PUL instrument is ongoing. Application of Rasch analysis using the two clinician-reported outcome scales, both of which represent different aspects of mobility, strongly suggests the utility of evaluating similarly constructed items from commonly used patient-reported instruments alone or in combination with clinically-obtained assessments.

1.1.7 Item list-specific recommendations for instrument development.

Using the Rasch analysis-derived feedback on item syntax and response category characteristics, and using the three clinical measurement instruments as guides to examine other possible elements of mobility function specific to DMD, as well as possible mobility functions that may exist outside of our currently appreciated ceiling and floor effects, we can make specific recommendations regarding future modifications of each mobility domain item list.

Walking and Moving: In the walking and moving list, we see that there are several high-residual items from the PODCI instrument. In addition, we have multiple items from the NeuroQoL that are missing a "Can't Do" response category. As discussed above, we should consider revising the question set so that items follow a format so that items are phrased as "In the past 7 days, I could _____" (responses With no trouble, With some trouble, With a lot of trouble, Can't do). This rephrasing should help to improve disordered responses by reducing ambiguity in the light to moderate difficulty responses, and may also help somewhat in extending the "floor" of the scale by accounting for individuals who cannot do the tasks. The title of the scale itself dictates the items that it addresses, and "Walking and moving" as a construct related to strength really only applies to those who are ambulatory to some degree. Wheelchair mobility items, on the whole, are not sensitive to changes in disease status / milestone, at least as defined here. Some of the questions we evaluated are aimed at manual wheelchair use, and some at power wheelchair use, and it's likely that there's a differential response between users of one technology vs. another, though we don't have the data to examine this here. There is likely a relationship with distal/hand ability and wheelchair driving, but technologies related to power wheelchair mobility are continuously evolving, and even individuals with very severe strength limitation are generally able to move about in their power chairs fairly easily. Wheelchair mobility should be a topic of discussion in future instrument development, to see whether any important topic areas emerge, and to develop some pilot questions. It also remains unclear whether wheelchair mobility, as an activity that is dictated by access to technology rather than disease progression specifically, represents a true physical mobility domain or more accurately reflects activity and participation – for example, it is hard to imagine that wheelchair mobility would be tested as an endpoint in a clinical trial of a drug to improve overall function. However, within the ambulatory group of patients, we can look to the North Star Ambulatory Assessment tool for suggestions on items that are easier (ie. to the left of the item

thresholds) to address floor effects, and more difficult items (ie. to the right of the item thresholds) to address ceiling effects. When compared to the NSAA (Table V.20), our questions address NSAA functions of running, walking, climbing a box step, and descending a box step. On the easier end of the spectrum, the NSAA grades the lowest level of walking function as Walking Grade 0: "Loss of independent ambulation – may use KAFOs or walk short distances with assistance." Our most difficult question "I could walk between rooms" is from the NeuroQOL and thus the most difficult response was "With a lot of trouble". As suggested by the NSAA scoring paradigm, addition of a "Can't do" response as noted above may then be expected to lower the "floor" of the instrument somewhat. On the most difficult end of the spectrum, our hardest question is "Walk more than a mile". Here it is instructive to look at the NSAA items (Table V.21) that are not represented in our current list, including jumping, hopping, standing on the heels, standing on one leg, and lifting the head while supine – all functions that have been noted as early deficits in children with DMD, and which may show to be more difficult than a one-mile walk. With the exception of the last item (lifting the head), all of these functions appear at face value to relate directly in some way to ambulatory ability – a model that has been validated by Mayhew and colleagues through their Rasch analysis of the NSAA instrument. Some children with DMD never attain the ability to hop on one foot, and thus addition of questions targeted to these four functions thus may extend the range of the question set to cover the entire young and more functional end of the DMD spectrum. From a standpoint of simplification and consolidation of multiple questions into a single item with responses directed at multiple levels of ability, it may be helpful for us to look at how the questions in our subscale are related to the items in the clinical scale (Table V.20). For instance, our question items that fall under the NSAA Item 6 and 7: Climbing and Descending steps domain may be appropriate to consolidate into a single item that reflects to perform climbs of increasing height and/or duration.

Table V.20. Items linking the North Star Ambulatory Assessment and the Walking and Moving Scale.

NSAA Item 2: Walking.

- 2 - Walks with heel-toe or flat-footed gait pattern
- 1 - Persistent or habitual toe walker, unable to heel-toe consistently
- 0 - Loss of independent ambulation – may use KAFOs or walk short distances with assistance

Linking Items (In order of difficulty)

- | | | |
|-----|------------|-------------------------------------------------------------------------|
| Q5 | nqmobped05 | I could walk between rooms |
| Q13 | nqmobped21 | I could walk on slightly uneven surfaces (such as cracked pavement) |
| Q18 | nqmobped24 | I could walk on rough, uneven surfaces (such as lawns, gravel driveway) |
| Q17 | posna_q44 | Walk one block? |
| Q1 | nqmobped01 | I could keep my balance while walking for 30 minutes |
| Q4 | nqmobped04 | I could walk for 15 minutes |
| Q19 | nqmobped25 | I could walk up and down ramps or hills |
| Q16 | posna_q43 | Walk three blocks? |
| Q6 | nqmobped12 | I could walk for 30 minutes |
| Q14 | posna_q42 | Walk more than a mile? |

NSAA Item 6, 7: Climb Box Step

- 2 - Faces step – no support needed
- 1 - Goes up sideways or needs support
- 0 - Unable

NSAA Items 8, 9: Descend Box Step

- 2 - Faces forward, climbs down controlling weight bearing leg. No support needed
- 1 - Sideways, skips down or needs support
- 0 - Unable

Linking Items

- | | | |
|-----|------------|--------------------------------|
| Q20 | nqmobped26 | I could walk up and down curbs |
| Q12 | posna_q41 | Climb one flight of stairs? |
| Q23 | nqmobped39 | I could walk up 2-3 stairs |
| Q9 | posna_q40 | Climb three flights of stairs? |

NSAA Item 17: Run (10m)

- 2 - Both feet off the ground (no double stance phase during running)
- 1 - 'Duchenne jog'
- 0 - Walk

Linking Item

- | | | |
|----|-----------|----------------------|
| Q7 | posna_q38 | Run short distances? |
|----|-----------|----------------------|

Table V.21. Functions from NSAA that are missing in the Walking and Moving item list.

NSAA Item 5: Stand on one leg.

- 2 - Able to stand in a relaxed manner (no fixation) for count of 3 seconds
- 1 - Stands but either momentarily or needs a lot of fixation e.g. by knees tightly adducted or other trick
- 0 - Unable

NSAA Item 12: Lifts head

- 2 - In supine, head must be lifted in mid-line. Chin moves toward chest
- 1 - Head is lifted but through side flexion or with no neck flexion
- 0 - Unable

NSAA Item 13: Stands on heels

- 2 - Both feet at the same time, clearly standing on heels only (acceptable to move a few steps to keep balance) for count of 3
- 1 - Flexes hip and only raises forefoot
- 0 - Unable

NSAA Item 14: Jump

- 2 - Both feet at the same time, clear of the ground simultaneously
- 1 - One foot after the other (skip)
- 0 - Unable

NSAA Item 15, 16: Hop

- 2 - Clears forefoot and heel off floor
- 1 - Able to bend knee and raise heel, no floor clearance
- 0 - Unable

Changing and Maintaining Body Position: In the changing and maintaining body position list, we see that there are several high-residual instruments from the PODCI instrument. In addition, we have multiple items from the NeuroQoL that are missing a "Can't Do" response category. As discussed above, we should consider revising the question set so that items follow a format so that items are phrased as "In the past 7 days, I could _____" (responses With no trouble, With some trouble, With a lot of trouble, Can't do). This rephrasing should help to improve disordered responses by reducing ambiguity in the light to moderate difficulty responses, and may also help somewhat in extending the "floor" of the scale by accounting for individuals who cannot do the tasks. Extension of the "floor" of the scale may also be informed through comparison of the current question items to items contained in the EK scale (Table V.22). When compared to the EK scale, our questions address functions of standing, transferring to and from a wheelchair, balancing in a wheelchair (or chair), moving the arms, turning in bed, and head control. On the easier end of the spectrum, the EK scale grades the lowest level of head control as Head Control Grade 3 – "When sitting still in a wheelchair needs head support". Our most difficult question "I could turn my head all the way to the side to look at someone or something" is from the NeuroQoL and thus the most difficult response was "With a lot of trouble". As we have previously noted, addition of a "Can't do" response may then be expected to lower the "floor" of the instrument somewhat. In addition, it is instructive to look at the other high-difficulty responses from the EK scale questions that are represented here. Other difficult items that might lower the instrument floor might include items from the wheelchair transfer question (Grade 2 – Needs assistance to transfer with or without additional aids; Grade 3 – Needs to be lifted with support of the head when transferring from wheelchair), Ability to balance in the wheelchair (Grade 3 – Unable to change position of the upper part of the body, cannot sit without total support of the trunk or head), Ability to turn in bed (Grade 2 – Unable to turn himself in bed. Has to be turned 0-3 times per night; Grade 3 – Unable to turn himself in bed, Has to be turned >4 times per night), and head control (Grade 3 – When sitting still in a wheelchair needs head support). Other items in the EK scale that are not represented in this question set (Table V.23) are primarily concerned with other functions not directly related to body position control but that may be instructive when considering hand and arm function (refer to the next section). On the most difficult end of the spectrum, our hardest question is "I could get on and off a chair without using my arms". The EK scale was developed as a tool for non-ambulatory individuals, and thus in this instance is not very informative. However when we examine disease-related milestones we can see that loss of the ability to stand from supine precedes loss of ability to rise from a chair, and thus the NSAA item 11: Rise from floor becomes relevant, as rising from supine can be considered a positional transfer. Addition of an item on the "difficult" end of the scale that addresses not only overall ability to rise from the floor, but the quality of such a motion may extend the "ceiling" of the instrument in the direction of more functional individuals. A question such as "In the past 7 days, I could stand from the floor without putting my hands on my knees" (responses With no trouble, With some trouble, With a lot of trouble, Can't do) might be effective at identifying children who can still stand without evidence of the classic "Gower's manoeuvre" that is an

early tell tale sign of early disease progress. From a standpoint of simplification and consolidation of multiple questions into a single item with responses directed at multiple levels of ability, it may be helpful for us to look at how the questions in our subscale are related to the items in the clinical scale (Table V.22). For instance, our bed, chair or toilet question items that fall under the EK Item 2: Ability to transfer from wheelchair domain may be appropriate to consolidate into a single item that reflect similar transfers of varying degrees of difficulty.

TABLE V.22. Items linking the NSAA and EK Scale and the Changing and Maintaining Body Position item list.

NSAA Item 11: Rise from floor

- 2 – From supine, no evidence of Gower's manoeuvre
- 1 – Gower's evident
- 0 – Needs external support object (eg. Chair) or unable

Linking Items

Q9 nqmobped13 I could get up from the floor by myself

EK Item 2: Ability to transfer from wheelchair

- 0 – Able to transfer from wheelchair without help
- 1 – Able to transfer independently from wheelchair, with use of aid
- 2 – Needs assistance to transfer with or without additional aids (hoist, easy-glide)
- 3 – Needs to be lifted with support of the head when transferring from wheelchair

Linking Items

Q24 nqexped31 I was able to get into bed by myself.
 Q23 posna_q28 Get in and out of bed?
 Q22 nqexped30 I was able to get out of bed by myself.
 Q2 nqwchped04 I could move between my wheelchair and another seat such as a chair or bed
 Q3 nqwchped06 I could manage getting on and off the tub bench from a wheelchair
 Q4 nqwchped07 I could manage getting on and off the toilet from a wheelchair
 Q5 nqwchped08 I could stand up from an armless straight chair using my wheelchair
 Q7 nqmobped10 I could get in and out of an adultsized chair
 Q21 posna_q27 Get on and off a toilet or chair?
 Q6 nqmobped09 I could get on and off a low chair
 Q8 nqmobped11 I could get on and off a chair without using my arms.

EK Item 3: Ability to Stand

- 0 – Able to stand with knees supported, as when using braces
- 1 – Able to stand with knees and hips supported, as when using standing aids
- 2 – Able to stand with full body support
- 3 – Unable to stand or be stood

Linking Items

Q19 posna_q25 Stand while washing his hands and face at a sink?
 Q27 posna_q31 How often did your child need help from another person for sitting and standing?

EK Item 4: Ability to balance in the wheelchair

- 0 – Able to push himself upright from complete forward flexion by pushing up with hands
- 1 – Able to move the upper part of the body >30 degrees in all directions from the upright position, but cannot push himself upright as above
- 2 – Able to move the upper part of the body <30 degrees from one side to the other
- 3 – Unable to change position of the upper part of the body, cannot sit without total support of the trunk or head.

Linking Items

Q11 nqmobped15 I could sit on a bench without back support for 30 minutes

EK Item 5: Ability to move the arms

- 0 – Able to raise the arms above the head with or without compensatory movements
- 1 – Unable to lift the arms above the head, but able to raise the forearms against gravity (ie. hand to mouth with/without elbow support)
- 2 – Unable to lift the forearms against gravity, but able to use the hands against gravity when the forearm is supported
- 3 – Unable to use the hands against gravity, but able to use the fingers

Linking Items

Q16 nqexped21 I was able to cover my nose when sneezing

EK Item 7: Ability to turn in bed

- 0 – Able to turn himself in bed when under bed sheets or cover
- 1 – Needs some help to turn in bed or can turn in some directions
- 2 – Unable to turn himself in bed. Has to be turned 0-3 times per night.
- 3 – Unable to turn himself in bed. Has to be turned >4 times per night.

Linking Items

Q12 nmd_q16 It is hard to turn myself during the night.
 Q17 nqexped26 I was able to change positions in my bed

EK Item 12: Head control

- 0 – Does not need head support
- 1 – Needs head support when going up and down slope (15 degree standard ramp)
- 2 – Needs head support when driving wheelchair
- 3 – When sitting still in a wheelchair needs head support

Linking Items

Q15 nqmobped19 I could turn my head all the way to the side to look at someone or something

Table V.23. Functions from the EK Scale that are missing in the Changing and Maintaining Body Position item list.

- EK Item 1: Ability to Use a Wheelchair
- 0 – Able to use a manual wheelchair on flat ground (10m < 1 minute)
 - 1 – Able to use a manual wheelchair on flat ground (10m > 1 minute)
 - 2 – Unable to use manual wheelchair, requires power wheelchair
 - 3 – Uses power wheelchair, but occasionally has difficulty steering
- EK Item 6: Ability to use hands and arms for eating
- 0 – Able to eat and drink without elbow support
 - 1 – Eats or drinks with support at elbow
 - 2 – Eats and drinks with elbow support; with reinforcement of the opposite hand + or – aides
 - 3 – Has to be fed
- EK Item 8: Ability to cough
- 0 – Able to cough effectively
 - 1 – Has difficulty to cough and sometimes needs manual reinforcement. Able to clear throat.
 - 2 – Always needs help in coughing. Only possible to cough in certain positions.
 - 3 – Impossible to cough, needs suction and/or hyperventilation techniques or IPPB in order to keep airways clear
- EK Item 9: Ability to speak
- 0 – Powerful speech, able to sing and speak loudly
 - 1 – Speaks normally, but cannot raise his voice
 - 2 – Speaks with a quiet voice, and needs a breath after 3-5 words
 - 3 – Speech is difficult to understand, except to close relatives
- EK Item 10: Physical well-being
- 0 – No complaints, feels good
 - 1 – Easily tires, has difficulty resting in a chair or bed
 - 2 – Has loss of weight, loss of appetite, scared of falling asleep at night, sleeps badly
 - 3 – Experiences additional symptoms: change of mood, stomach ache, palpitations, perspiring
- EK Item 11: Daytime fatigue
- 0 – Doesn't get tired during the day
 - 1 – Need to limit activity to avoid getting too tired
 - 2 – Need to limit activity and have a rest period to avoid getting too tired
 - 3 – Get tired during the day even if I rest and limit activity
- EK Item 13: Ability to control joystick
- 0 – Uses a standard joystick without adaptation
 - 1 – Uses an adapted joystick or has adjusted wheelchair in order to use joystick
 - 2 – Uses other techniques for steering than joystick such as blowing sucking systems or scanned driving
 - 3 – Unable to operate wheelchair, needs another person to operate it
- EK Item 14: Food Textures
- 0 – Eats all textures of food
 - 1 – Eats cut up/chunky food or avoids hard/chewy foods
 - 2 – Eats minced/pureed food with supplementation as required
 - 3 – Main intake consists of being tube fed
- EK Item 15: Eating a meal
- 0 – Able to consume a whole meal in the same time as others sharing the meal
 - 1 – Able to consume a whole meal in the same time as others only with encouragement or needs some additional time (approximately 10 minutes)
 - 2 – Able to consume a whole meal but requires substantially more time compared to others eating the same meal (15 minutes or more extra)
 - 3 – Unable to consume a whole meal
- EK Item 16: Swallowing
- 0 – Never has problems when swallowing, and never chokes on food/drink
 - 1 – May experience occasional (less than once a month) problems swallowing certain types of food or occasionally chokes
 - 2 – Has regular trouble swallowing food/drink or chokes on food/drink (more than once a month)
 - 3 – Has trouble swallowing saliva or secretions
- EK Item 17: Hand function
- 0 – Can unscrew the lid of a water or fizzy drink bottle and can break the seal
 - 1 – Can write two lines or use the computer keyboard
 - 2 – Can write signature or send text or use remote control
 - 3 – Cannot use hands

Carrying, Moving and Handling Objects: In the carrying, moving and handling objects list, we once again see that there are high-residual instruments from the PODCI instrument. In addition, we have multiple items from the NeuroQoL that are missing a "Can't Do" response category. As discussed above, we should consider revising the question set so that items follow a format so that items are phrased as "In the past 7 days, I could _____" (responses With no trouble, With some trouble, With a lot of trouble, Can't do). This rephrasing should help to improve disordered responses by reducing ambiguity in the light to moderate difficulty responses, and may also help somewhat in extending the "floor" of the scale by accounting for individuals who cannot do the tasks. Extension of the "floor" of the scale may also be informed through comparison of the current question items to items contained in the PUL Assessment (Table V.24). When compared to the PUL Assessment, our questions address functions of lifting heavy weights, opening containers, holding items while supinating the hand, and fine motor ability. On the more difficult end of the spectrum, the PUL assessment contains multiple hand functions relating to fine motor control that may fall below our weakest items of "It's hard to use my hands" (Table V.25). These items include tearing paper, tracing a path with a pencil, pushing on a light switch, placing a finger on a number diagram, and pinch, 3-point and thumb grips. All of these functions are maintained until very late in disease progression, and developing questions to address similar daily tasks would be expected to extend the "floor" of our instrument to a much larger number of very weak individuals. In fact, recent Rasch analysis results of the development of the Person Reported Measure Upper Limb (PROM UL) by Katrijn Klingel (PROM-UL development group meeting, June 10 2015) reveal a list of upper extremity functional tasks that extend far past our current set of items on the weak end of the spectrum. Question items, which range from "Screw the cap off a bottle that has not been opened before" (strong end) to "Use a TV remote control" are presented in Table V.26. In her presentation, Dr. Klingel noted an outlier group on the stronger end of the scale. This makes sense when we combine our list and the PROM-UL items in order from easiest to most difficult (Table V.27). We see that the order of tasks is somewhat in agreement, with considerable overlap in the middle of the spectrum. As noted, PROM-UL items cover the weaker end of the spectrum, and our items cover the stronger end. We still observe a ceiling effect that produces outlier individuals on the stronger end of the spectrum. However, in considering additional questions on the stronger end, we may be able to look to the PUL Assessment items that evaluate shoulder function, namely shoulder abduction and flexion to at or above shoulder height, and identify daily activities that might require that type of motion. These may involve high level tasks such as brushing hair, scratching the top of the head, or reaching for highly placed objects. Some of the shoulder-height tasks may already be represented by our questions regarding ability to open doors (doorknobs are often at shoulder height for children and individuals in wheelchairs), but that will require further evaluation. From a standpoint of simplification and consolidation of multiple questions into a single item with responses directed at multiple levels of ability, it may again be helpful for us to look at how the questions in our subscale are related to the items in the clinical scale (Table V.25). For instance, our container opening question items that fall under the PUL Item M: Remove lid from container heading may be

appropriate to consolidate into a single item that reflect similar tasks of varying degrees of difficulty.

Table V.24. Items linking the PUL and the Changing and Carrying, Moving and Handling Objects item list.

PUL Item H: Move weight on table

- 5 - Can lift 1kg weight from outer to centre circle without compensation
- 4 - Can lift 500g weight from outer to centre circle without compensation
- 3 - Can lift 200g weight from outer to centre circle without compensation
- 2 - Can lift 100g weight from outer to centre circle without compensation
- 1 - Can slide 100g weight from outer to centre circle without compensation
- 0 - Unable

Linking Items

- Q5 phys_q4 Lifting something heavy
- Q1 posna_q7 Lift heavy books?

PUL Item J: Lifting Heavy Cans

- 5 - Lift 5 (furthest away from preferred) [Note this is across body midline]
- 4 - Lift 4
- 3 - Lift 3 (Centre)
- 2 - Lift 2
- 1 - Lift 1 (Outer)
- 0 - Unable

Linking Items

- Q6 nquexped08 I was able to hold a full cup of water in my hand.
- Q3 posna_q8 Pour a half gallon of milk?
- Q13 nquexped17 I was able to pick up a gallon of milk with one hand and set it on the table

PUL M: Remove Lid from Container

- 1 - Opens completely
- 0 - Unable to open

Linking Items

- Q2 nquexped01 I was able to open small containers like snack bags or vitamins (regular screw top)
- Q17 nquexped23 I was able to open a can of soda
- Q4 posna_q9 Open a jar that's been opened before?
- Q19 nquexped33 I was able to open a jar by myself.

PUL Item Q: Supination

- 4 - Picks up the light, and turns the hand over completely without any compensatory movements
- 3 - Picks up the light and turns it over completely with compensatory movements
- 2 - Picks up the light and turns the hand over incompletely
- 1 - Picks up the light but cannot turn the hand over
- 0 - Cannot pick up the light

Linking Items

- Q10 nquexped15 I was able to hold a plate full of food

PUL Item R: Picking up coins

- 3 - Can pick up and hold six coins in one hand
- 2 - Can pick up and hold three coins in one hand
- 1 - Can pick up one coin
- 0 - Cannot pick up one coin

Linking Items

- Q8 nmd_q11 It is hard to use my hands.
- Q7 nmd_q8 My hands are weak.

Table V.25. Functions from the PUL Assessment that are missing in the Carrying, Moving and Handling Objects item list.

PUL Item B: Shoulder abduction to shoulder height

- 4 – 1000g
- 3 – 500g
- 2 – 200g
- 1 – Able, no weights
- 0 – Unable

PUL Item C: Shoulder abduction above shoulder height

- 4 – 1000g
- 3 – 500g
- 2 – 200g
- 1 – Able, no weights
- 0 – Unable

PUL Item D: Shoulder flexion to shoulder height

- 4 – 1000g
- 3 – 500g
- 2 – 200g
- 1 – Able, no weights
- 0 – Unable

PUL Item D: Shoulder flexion above shoulder height

- 4 – 1000g
- 3 – 500g
- 2 – 200g
- 1 – Able, no weights
- 0 – Unable

PUL Item F: Hand to mouth

- 3 – Able to bring 200g in cup to mouth with one hand and no elbow support
- 2 – Able to bring 200g in cup to mouth either with 2 hands or one hand with elbow support
- 1 – Able to bring 50g in cup to mouth using 2 hands
- 0 – Unable

PUL Item G: Hand(s) to table from lap

- 3 – Two hands completely and simultaneously to table
- 2 – Two hands completely on table but not at same time
- 1 – Gets both hands on table but incompletely
- 0 – Unable

PUL Item I: Lifting light cans

- 5 – Lift 5 (furthest away from preferred) [Note this is across body midline]
- 4 – Lift 4
- 3 – Lift 3 (Centre)
- 2 – Lift 2
- 1 – Lift 1 (Outer)
- 0 – Unable

PUL Item K: Stacking Light Cans

- 5 – Stack 5th can
- 4 – Stack 4th can
- 3 – Stack 3rd can
- 2 – Stack 2nd can
- 1 – Unable to stack 2nd can

PUL Item L: Stacking Heavy Cans

- 5 – Stack 5th can
- 4 – Stack 4th can
- 3 – Stack 3rd can
- 2 – Stack 2nd can
- 1 – Unable to stack 2nd can

PUL Item N: Tearing paper

- 4 – Tears the sheet of paper folded in 4, beginning from the fold edge
- 3 – Tears the sheet of paper folded in 2, beginning from the fold edge
- 2 – Tears the unfolded sheet of paper
- 1 – Can hold unfolded sheet of paper but cannot tear it
- 0 – Cannot hold paper or tear it

PUL Item O: Tracing path

- 4 – Able to pick up pencil and able to complete the path without stops or raising hand from paper
- 3 – Able to complete the path but needs to stop or raises hand from paper
- 2 – Able to follow the path for at least 5cm but unable to complete the path
- 1 – Able to hold pencil and can make a mark on the paper
- 0 – With pencil in hand unable to hold it or to make a mark

PUL Item P: Push on the light

- 3 – Able to turn the light on permanently with one hand
- 2 – Able to turn the light on momentarily with one hand
- 1 – Able to turn the light on momentarily with two hands
- 0 – Unable to turn the light on momentarily with two hands

PUL Item S: Place finger on number diagram

- 3 – Raises finger and places it successively on the numbers of the diagram without touching the lines
- 2 – Raises finger and places it imprecisely on the numbers
- 1 – Cannot raise finger to place it on a drawing but can slide it between at least two squares
- 0 – Cannot raise finger or slide it on the diagram

PUL Item T: Finger pinch grip

- 2 – Able to finger pinch and lift weight
- 1 – Able to achieve finger pinch grip but can't move weight
- 0 – Unable to achieve finger pinch grip

PUL Item U: 3 point grip

- 2 – Able to 3 point grip and lift weight
- 1 – Able to achieve 3 point grip but can't move weight
- 0 – Unable to achieve 3 point grip

PUL Item V: Thumb (key) grip

- 3 – Able to grip and lift weight
- 2 – Able to achieve thumb grip but can't lift weight
- 1 – Unable to achieve thumb grip but can move end of thumb
- 0 – Unable to achieve thumb grip or bend end of thumb

Table V.26: PROM Items by Order of Difficulty, easiest to hardest (Katrijn Klingels' slide presentation, Rome UL meeting, June 10, 2015)

Use a TV remote control
Use a mouse
Type on a computer with a keyboard
Sign name
Turn the pages of a book
Pick up small objects from the table
Dial/Text on a cell phone (this may be adapted to "use a touchscreen")
Eat a meal
Press buttons on an elevator
Open a drawer
Turn a light switch on/off on the wall at a standard height
Drink from a half-full glass without a straw
Reach out to shake hands
Bring a phone to your ear
Wash hands
Write several lines
Wipe nose
Brush teeth
Take money from a wallet from your pocket to pay for something
Scratch head
Take a book out of a bag on your lap
Open a fridge door
Open a pack of crisps (chips)
Pour a drink from a half-liter bottle
Fasten a zipper
Cut up different textures of food
Pick up a pen from the floor
Put a jacket on
Button up (a shirt for example)
Pull up trousers after using the toilet
Open a can of soft drink
Screw the cap off a bottle that has not been opened before

Table V.27: Combined items from the Carrying, Moving and Handling Objects scale and the experimental PROM-UL device (bold), in apparent order from easiest to most difficult

Use a TV remote control
 Use a mouse
 Type on a computer with a keyboard
 Sign name
 Turn the pages of a book
 Pick up small objects from the table
 Dial/Text on a cell phone (this may be adapted to "use a touchscreen")
 Q8 nmd_q11 It is hard to use my hands.
 Q6 nquexped08 I was able to hold a full cup of water in my hand.
 Q15 ngwchped19 I could manage the armrests on my wheelchair
 Q9 nquexped12 I was able to use a knife to spread butter or jelly on bread
 Eat a meal
 Q18 posna_q29 Turn doorknobs?
 Q14 nquexped19 I was able to cut a piece of paper in half with scissors
 Press buttons on an elevator
 Open a drawer
 Turn a light switch on/off on the wall at a standard height
 Drink from a half-full glass without a straw
 Reach out to shake hands
 Bring a phone to your ear
 Wash hands
 Write several lines
 Wipe nose
 Brush teeth
 Take money from a wallet from your pocket to pay for something
 Scratch head
 Take a book out of a bag on your lap
 Open a fridge door
 Q2 nquexped01 I was able to open small containers like snack bags or vitamins (regular screw top)
 Open a pack of crisps (chips)
 Pour a drink from a half-liter bottle
 Fasten a zipper
 Cut up different textures of food
 Pick up a pen from the floor
 Put a jacket on
 Button up (a shirt for example)
 Pull up trousers after using the toilet
 Q7 nmd_q8 My hands are weak.
 Q16 ngwchped20 I could manage the footrests on my wheelchair.
 Q4 posna_q9 Open a jar that's been opened before?
 Open a can of soft drink
 Q17 nquexped23 I was able to open a can of soda
 Q11 ngwchped16 I could open a door that faced away from my wheelchair
 Q12 ngwchped17 I could open a door that was facing my wheelchair
 Q21 nquexped37 I was able to open the rings in school binders.
 Q10 nquexped15 I was able to hold a plate full of food
 Screw the cap off a bottle that has not been opened before
 Q19 nquexped33 I was able to open a jar by myself.
 Q3 posna_q8 Pour a half gallon of milk?
 Q1 posna_q7 Lift heavy books?
 Q20 nquexped36 I was able to pull open heavy doors.
 Q13 nquexped17 I was able to pick up a gallon of milk with one hand and set it on the table

What opportunities for training and professional development has the project provided?

If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. “Training” activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. “Professional development” activities result in increased knowledge or skill in one’s area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to Report

How were the results disseminated to communities of interest?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to Report

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

Nothing to Report

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Commonly-employed PROs and Clinically-Reported Outcome Measures (ClinROs) used in DMD research have been noted to apply only to subsets of individuals with respect to age and level of mobility/ability. We have developed prototype mobility question sets that span a range of mobility represented across the lifespan of individuals with DMD, and that are responsive to disease progression over a one-year period of time frequently employed in DMD clinical trials. Next steps will include refinement of these tools to address noted ceiling and floor effects, and collection of pilot data to evaluate device validity and responsiveness.

What was the impact on other disciplines?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to Report

What was the impact on technology transfer?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Data from the CINRG DMD natural history study cohort will provide the basis for development of a “clinical trial-ready” novel lifespan-oriented computer adaptive testing-based PRO measure that has been constructed against a background of comprehensive clinical assessments of strength and function across the DMD lifespan. This PRO measure will be rapidly deployable as a sensitive measure for use in the growing field of DMD clinical trials.

What was the impact on society beyond science and technology?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- improving public knowledge, attitudes, skills, and abilities;*
- changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- improving social, economic, civic, or environmental conditions.*

Nothing to Report

- 5. CHANGES/PROBLEMS:** The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, “Nothing to Report,” if applicable:

Changes in approach and reasons for change

Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

We experienced initial delays in receipt of Person-Reported Outcome Measure data from the UC Davis/CINRG Duchenne Natural History Study (DNHS). This delay stemmed from two sources. First, the DNHS has become a major resource for academic and industry investigators, providing disease progression and outcome measure performance data that is being used in support of new study designs and data analysis efforts. Because of this, there was a significant wait for processing of our project data request and subsequent production of our dataset. Second, there were further delays in the production of our dataset due to a comprehensive re-characterization of glucocorticoid steroid use in our study participants. This detailed characterization (described by Bello et al, 2015) required full clinical histories and updated data on all study participants. We elected to wait for the completion of that data collection prior to production of our final dataset. No further delays have been encountered.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to Report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Nothing to Report

Significant changes in use or care of vertebrate animals

Nothing to Report

Significant changes in use of biohazards and/or select agents

Nothing to Report

6. PRODUCTS: List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- Publications, conference papers, and presentations**

Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to Report

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to Report

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to Report

- **Website(s) or other Internet site(s)**

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to Report

- **Technologies or techniques**

Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to Report

- **Inventions, patent applications, and/or licenses**

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to Report

- **Other Products**

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*
- *physical collections;*
- *audio or video products;*
- *software;*

- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate “no change”.

Example:

Name: Mary Smith
Project Role: Graduate Student
Researcher Identifier (e.g. ORCID ID): 1234567
Nearest person month worked: 5
Contribution to Project: Ms. Smith has performed work in the area of combined error-control and constrained coding.
Funding Support: The Ford Foundation (Complete only if the funding support is provided from other than this award.)

Name: Craig McDonald, MD (PI) - No Change
 Name: Erik Henricson, MPH (Co-Investigator) - No Change
 Name: Nanette Joyce, DO (Co-Investigator) - No Change
 Name: Anital Bagley, PhD, MPH (Co-Investigator) - No Change
 Name: Evan deBie, BS (Data Manager) – No Change
 Name: Erica Goude, MS (Outreach Coordinator) - No Change
 Name: Mary Jane Mulcahey, PhD (Co-Investigator) – No Change

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Active support has changed for the PI (McDonald) and co-investigators (Henricson and Joyce). The main change is the successful completion of the U.S. Department of Education Grant “Rehabilitation Research & Training Center – Enhancing Health & Wellness of Individuals with Neuromuscular Disease (McDonald) (H133B090001)”. Subsequent changes in overall effort are provided in the Appendix as revised “Other Support” documents for each investigator. In addition, Mr. Henricson has reduced his time commitment on the award “NINDS Network for Excellence in Neuroscience: Clinical Research Site at UC Davis (McDonald) (1U10NS077422)”.

What other organizations were involved as partners?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:

Organization Name:

Location of Organization: (if foreign location list country)

Partner’s contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner’s facilities for project activities);*
- *Collaboration (e.g., partner’s staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner’s staff use each other’s facilities, work at each other’s site); and*
- *Other.*

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to <https://ers.amedd.army.mil> for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on <https://www.usamraa.army.mil>) should be updated and submitted with attachments.

9. **APPENDICES:** Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

Appendix 1: REFERENCES

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- Henricson, E., R. Abresch, J. J. Han, A. Nicorici, E. Goude Keller, E. de Bie and C. M. McDonald (2013). "The 6-minute walk test and person-reported outcomes in boys with duchenne muscular dystrophy and typically developing controls: longitudinal comparisons and clinically-meaningful changes over one year." PLoS Curr **5**.
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